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(57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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CDNAS ENCODING SECRETED PROTEINS

The extended cDNAs of the present invention were described in several U.S. Provisional Patent applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced. Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mislabeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include portions of the coding sequence of the gene from which the EST

was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3′ untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3′ end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5′ ends of mRNAs. (Adams et al., *Nature* **377**:174, 1996, Hillier et al., *Genome Res.* **6**:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported sequences typically correspond to coding sequences and do not include the full 5′ untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5′ ends of mRNAs which can be used to obtain extended cDNAs which may include the 5′ sequences contained in the 5′ ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon-α, interferon-β, interferon-γ, and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences located at the 5′ ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides also find application in simplifying protein purification techniques. In such

applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5′ portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al., Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing SpeI binding sites by the use of SpeI binding protein. (Mortlock et al., *Genome Res.* 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

5′ ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil *et al.*, *BioFactors* 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5′ ends of secretory protein genes or extended cDNAs which include sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5′ coding sequences of genes encoding secretory proteins.

Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5′ ends of their corresponding mRNAs. As used herein the terms "EST" or "5′ EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5′ EST used to obtain them. The extended cDNAs may contain all or a portion of the sequence of the EST which was used to obtain them. The

term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10^4-10^6 fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are " enriched recombinant extended cDNAs" as defined herein. However, extended cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in

which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal peptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the

translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-84 and 130-154 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-84 and 130-154 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-84 and 130-154 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-84 and 130-154 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-84 and 130-154. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID Nos: 40-84 and 130-154 wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40-59,

61-73, 75, 77-82, and 130-154 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-84 and 130-154 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEQ ID NOs: 40-59, 61-75, 77-82, and 130-154 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-84 and 130-154 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEQ ID NOs: 40-59, 61-73, 75-82, 84, and 130-154 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 85-129 and 155-179.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 85-129 and 155-179. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 85-104, 106-120, 122-127, and 155-179.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 85-129 and 155-179. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 85-104, 106-118, 120-127, 129, and 155-179.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 85-129 and 155- 179.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 85-129 and 155- 179. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive amino acids of one of the sequences of SEQ ID NOs: 85-129 and 155- 179. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 85-129 and 155- 179.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 85-129 and 155- 179. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 85-104, 106-118, 120-127, 129, and 155-179.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 85-129 and 155- 179. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 85-104, 106-120, 122-127, and 155-179. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 85-104, 106-120, 122-127, and 155-179.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 85-129 and 155-179, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-84 and 130-154, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NOs. 85-104, 106-120, 122-127 and 155-179, comprising the steps of obtaining a cDNA comprising one of the nucleotide sequences of SEQ ID Nos. 40-59, 61-75, 77-82 and 130-154 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NOs: 85-104, 106-120, 122-127, and 155-179 comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NOs: 40-59, 61-75, 77-82, and 130-154 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-84 and 130-154 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEQ ID NOs: 40-59, 61-73, 75, 77-82, and 130-154, wherein the

full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-84 and 130-154 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-59, 61-75, 77-82, and 130-154 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-84 and 130-154 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID Nos.: 40-59, 61-73, 75-82, 84, and 130-154 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 85-129 and 155-179. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 85-129 and 155-179.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-84 and 130-154, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-84 and 130-154, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-84 and 130-154, the sequences complementary to the sequences of SEQ ID NOs: 40-84 and 130-154, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-84 and 130-154, the sequences complementary to the sequences of SEQ ID NOs: 40-84 and 130-154, or fragments thereof of at least 15 consecutive nucleotides.

A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 85-129 and 155-179, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to

be identical to a public sequence in any of Figures 10 to 12. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

Another embodiment of the present invention is a computer readable medium having stored thereon a sequence selected from the group consisting of a cDNA code of SEQID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179.

Another embodiment of the present invention is a computer system comprising a processor and a data storage device wherein the data storage device has stored thereon a sequence selected from the group consisting of a cDNA code of SEQID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179. In some embodiments the computer systme further comprises a sequence comparer and a data storage device having reference sequences stored thereon. For example, the sequence comparer may comprise a computer program which indicates polymorphisms. In other aspects of the computer system, the system further comprises an identifier which identifies features in said sequence.

Another embodiment of the present invention is a method for comparing a first sequence to a reference sequence wherein the first sequence is selected from the group consisting of a cDNA code of SEQID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179 comprising the steps of reading the first sequence and the reference sequence through use of a computer program which compares sequences and determining differences between the first sequence and the reference sequence with the computer program. In some embodiments of the method, the step of determining differences between the first sequence and the reference sequence comprises identifying polymorphisms.

Another embodiment of the present invention is a method for identifying a feature in a sequence selected from the group consisting of a cDNA code of SEQID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179 comprising the steps of reading the sequence through the use of a computer program which identifies features in sequences and identifying features in the sequence with said computer program.

Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5′ ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5′ ESTs in each of the categories described herein and the probability that these 5′ ESTs encode a signal peptide.

Figure 4 shows the distribution of 5′ ESTs in each category and the number of 5′ ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5′ ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. PED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. PED vectors are described in Kaufman et al. (1991), NAR 19:4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5′ tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

Figure 10 is an alignment of the proteins of SEQ ID NOs: 120 and 180 wherein the signal peptide is in italics, the predicted transmembrane segment is underlined, the experimentally determined transmembrane segment is double-underlined, and the ATP1G/PLMN/MAT8 signature is in bold.

Figure 11 is an alignment of the proteins of SEQ ID NOs: 121 and 181 wherein the predicted transmembrane segment is underlined.

Figure 12 is an alignment of the proteins of SEQ ID NOs: 128 and 182 wherein the PPPPY motif is in bold.

Detailed Description of the Preferred Embodiment

I. Obtaining 5′ ESTs

The present extended cDNAs were obtained using 5′ ESTs which were isolated as described below.

A. Chemical Methods for Obtaining mRNAs having Intact 5′ Ends

In order to obtain the 5′ ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5′ ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these approaches is a chemical modification method involving derivatization of the 5′ ends of the mRNAs and selection of the derivatized mRNAs. The 5′ ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5′, 5′-triphosphate bond. In some instances, the 5′ guanosine is methylated in both the 2 and 7 positions. Rarely, the 5′ guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5′ ends, the 5′ cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5′ end of the mRNA and the ribose linked to the base at the 3′ terminus of the mRNA, possess 2′, 3′-cis diols. Optionally, where the 3′ terminal ribose has a 2′, 3′-cis diol, the 2′, 3′-cis diol at the 3′ end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5′ end of the mRNA with a 2′, 3′-cis diol. A variety of techniques are available for eliminating the 2′, 3′-cis diol on the 3′ terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3′ terminal ribose is a 3′-phosphate, 2′-phosphate or (2′, 3′)-cyclophosphate. Thereafter, the fragment which includes the original 3′ ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2′, 3′-cis diol may be added to the 3′ end of the mRNA

using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3′ end of messenger RNA.

EXAMPLE 1

Ligation of the Nucleoside Diphosphate pCp to the 3′ End of Messenger RNA

1 µg of RNA was incubated in a final reaction medium of 10 µl in the presence of 5 U of T_4 phage RNA ligase in the buffer provided by the manufacturer (Gibco - BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2 µl of ^{32}pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2′, 3′-cis diol at the 3′ ribose, the 2′, 3′-cis diol present at the 5′ end of the mRNA may be oxidized using reagents such as $NaBH_4$, $NaBH_3CN$, or sodium periodate, thereby converting the 2′, 3′-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2′, 3′-cis diol at the 5′ end of the mRNA with sodium periodate.

EXAMPLE 2

Oxidation of 2′, 3′-cis diol at the 5′ End of the mRNA

0.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5′)ppp(5′)G. This compound, recognized by polymerase, was incorporated into the 5′ end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step. Consequently, the resulting RNA contained a cap at its 5′ end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:

+Cap:

5′m7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3′ (SEQ ID NO:1)

-Cap:

5′-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3′ (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

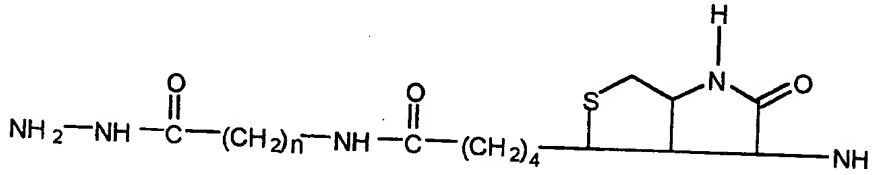
The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5′ ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5′

ends include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

EXAMPLE 3

Coupling of the Dialdehyde with Biotin

The oxidation product obtained in Example 2 was dissolved in 50 µl of sodium acetate at a pH of between 5 and 5.2 and 50 µl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:



In the compound used in these experiments, n=5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

EXAMPLE 4

Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with ^{32}pCp as described in Example 1.

Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with ^{32}pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with ^{32}pCp as described in Example 1.

Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with ^{32}pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the

slowest migration. The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5′ ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5′ ends may be released from the solid phase following the enrichment procedure. For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5′ ends following enrichment. Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the biotinylated mRNAs from the beads following enrichment.

EXAMPLE 5

Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 - 6). After incubating for 30 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

EXAMPLE 6

Efficiency of Recovery of Biotinylated mRNAs

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with ^{32}pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5′ ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3′ end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3′ end of the mRNA. For example, pCp may be attached to the 3′ end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3′ end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

EXAMPLE 7

Derivatization of the Oligonucleotide

An oligonucleotide phosphorylated at its 3′ end was converted to a 3′ hydrazide in 3′ by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula $H_2N(R1)NH_2$ at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3′ OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3′ OH, such as pCp, as described above in Example 1. Alternatively, the 3′ OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

EXAMPLE 8

Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100µl of 0.1N sodium hydroxide, 1.5µg mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3′ OH groups, the diol groups at the 5′ ends of the mRNAs are oxidized as described below in Example 9.

EXAMPLE 9

Oxidation of Diols

Up to 1 OD unit of RNA was dissolved in 9 µl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 µl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

Following oxidation of the diol groups at the 5′ ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

EXAMPLE 10

Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

EXAMPLE 11

Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5′-OH and 3′-P ends were dissolved in 70 µl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in $LiClO_4$/acetone. The pellet was resuspended in 200 µl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in $LiClO_4$/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

10 µl of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39 µl of 10 mM urea and 2 µl of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45 µm.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µl fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5′ end with ^{32}P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5′ end with ^{32}P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5′-P-P-P-5′ bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)

GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3′ (SEQ ID NO:6)

dehydrogenase

3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID NO:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

Non specific amplifications were also carried out with the antisense (_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.

Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.

Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the presence of cDNA.

Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.

Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.

Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.

Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.

Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEQ ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5′ ends. Further detail regarding the chemical approaches for obtaining mRNAs having intact 5′ ends are disclosed in International Application No. WO96/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5′ cap structure may be utilized to generate cDNAs which have been selected to include the 5′ ends of the mRNAs from which they are derived. In one version of such procedures, the 5′ ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5′ end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5′ end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5′ end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5′ end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. **Genomics** 37:327-336 (1996), may be employed to select cDNAs which include the sequence derived from the 5′ end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5′ cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5′ end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5′ ends of the mRNAs from which they are derived.

B. Enzymatic Methods for Obtaining mRNAs having Intact 5′ Ends

Other techniques for selecting cDNAs extending to the 5′ end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EP0 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate groups present on the 5′ ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3′ end, is then ligated to the phosphate present at the 5′ end of the decapped mRNA using T4 RNA ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

EXAMPLE 12

Enzymatic Approach for Obtaining 5′ ESTs

Twenty micrograms of PolyA+ RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5′DNA/RNA-3′ oligonucleotide having an unphosphorylated 5′ end, a stretch of adenosine ribophosphate at the 3′ end, and an EcoRI site near the 5′ end was ligated to the 5′P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5′ end may be synthesized by adding a fluorochrome at the 5′ end. The inclusion of a stretch of adenosine ribophosphates at the 3′ end of the oligonucleotide increases ligation efficiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5′ end of the decapped mRNA, first and second strand cDNA synthesis may be carried out using conventional methods or those specified in EP0 625,572 and Kato et al. Construction of a Human Full-Length cDNA Bank. **Gene** 150:243-250 (1994), and Dumas Milne Edwards, *supra*. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989.

II. Characterization of 5′ ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5′ ends were employed to obtain 5′ ESTs. First, mRNAs were prepared as described in Example 13 below.

EXAMPLE 13

Preparation of mRNA

Total human RNAs or PolyA+ RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., **Analytical Biochemistry** 162:156-159, 1987). PolyA+ RNA was isolated from total RNA (LABIMO) by two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., **Proc. Natl. Acad. Sci. USA** 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for enriching mRNAs having intact 5′ ends discussed above were employed to obtain 5′ ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5′ ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe complementary to the oligonucleotide tag.

EXAMPLE 14

cDNA Synthesis Using mRNA Templates Having Intact 5′ Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5′end of the ligated oligonucleotide described in Example 12. Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

EXAMPLE 15

Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the SmaI and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

EXAMPLE 16

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5′ EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., **Gene 127**:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The

resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., **Biotechniques, 13**: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3′ end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5′ tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

EXAMPLE 17

Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5′ end. If needed, these can easily be removed on a case by case basis.

Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5′ ESTs were entered in a proprietary database called NETGENE™ for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data. Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL), BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and peptide (BLASTX) comparisons (Altschul et al, **J. Mol. Biol. 215**: 403 (1990)) and FASTA (Pearson and Lipman, **Proc. Natl. Acad. Sci. USA, 85**: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn-helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

Before searching the cDNAs in the NETGENE™ database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

EXAMPLE 18

Elimination of Undesired Sequences from Further Consideration

5′ ESTs in the NETGENE™ database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5′ ESTs encoding tRNAs from further consideration, the 5′ EST sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5′ ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNA. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5′ ESTs encoding rRNAs from further consideration, the 5′ EST sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5′ ESTs with the parameter S=108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5′ ESTs encoding mtRNAs from further consideration, the 5′ EST sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5′ ESTs with the parameter S=108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5′ EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S=144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5′ ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5′ ESTs containing such repeat sequences from further consideration. 5′ ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained L1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats

depending on the source of the RNA which was used to prepare the cDNA library (Adams et al., *Nature* 377:174, 1996).

The sequences of those 5′ ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

EXAMPLE 19

Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5′ ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5′ ESTs to identify those matching an entry in the public human mRNA database. The 6655 5′ ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of "errors" which would be recognized. Errors occurring in the last 10 bases of the 5′ EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENE™ database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5′ ends of their corresponding mRNAs, the following analysis was performed.

EXAMPLE 20

Determination of Efficiency of 5′ EST Selection

To determine the efficiency at which the above selection procedures isolated 5′ ESTs which included sequences close to the 5′ end of the mRNAs from which they were derived, the sequences of the ends of the 5′ ESTs which were derived from the elongation factor 1 subunit α and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit α and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5′ ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5′ end of the corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5′ ESTs from ESTs in the NETGENE™ database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5′ ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5′ ends close to the 5′ ends of the known sequence. As some of the mRNA sequences available in the GenBank database are deduced from genomic sequences, a 5′ end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5′ ends of their corresponding mRNAs.

The EST libraries made above included multiple 5′ ESTs derived from the same mRNA. The sequences of such 5′ ESTs were compared to one another and the longest 5′ ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

EXAMPLE 21

Clustering of the 5′ ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5′ end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S=107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5′ end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR= 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5′ EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5′ ESTs in NETGENE™ was screened to identify those 5′ ESTs bearing potential signal sequences as described in Example 22 below.

EXAMPLE 22

Identification of Potential Signal Sequences in 5′ ESTs

The 5′ ESTs in the NETGENE™ database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST. Approximately half of the cDNA sequences in NETGENE™ contained such an ORF. The ORFs of these 5′ ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. **Nucleic Acids Res.** 14:4683-4690 (1986). Those 5′ EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5′ ESTs which matched a known human mRNA or EST sequence and had a 5′ end more than 20 nucleotides downstream of the known 5′ end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAG™.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

EXAMPLE 23

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5′ ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5′ region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5′ ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5′ ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5′ ESTs actually functions as a signal peptide, the signal sequences from the 5′ ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5′ EST encodes a genuine signal peptide, the signal sequence of the 5′ EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5′ EST inserted therein confirms that the 5′ EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequence-reporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which encode a functional signal peptide or an authentic secreted protein.

Those 5′ ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5′ ESTs is described in Example 24 below.

EXAMPLE 24

Categorization of 5′ ESTs Encoding a Signal Peptide

Those 5′ ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAG™ database, 947 of the 5′ ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5′ ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5′ direction. Of the sequences in the SIGNALTAG™ database, 150 of the 5′ ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the known EST by at least 40 nucleotides in the 5′ direction were designated "EST." Of the sequences in the SIGNALTAG™ database, 599 of the 5′ ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5′ ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5′ direction were designated "VERT-ext." Of the sequences in the SIGNALTAG™ database, 23 of the 5′ ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5′ EST which extended the known sequence of the human translocase mRNA by more than 200 bases in the 5′ direction. A 5′ EST which extended the sequence of a human tumor suppressor gene in the 5′ direction was also identified.

Figure 4 shows the distribution of 5′ ESTs in each category and the number of 5′ ESTs in each category having a given minimum von Heijne's score.

Each of the 5′ ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, as described below in Example 25.

EXAMPLE 25

Categorization of Expression Patterns

Figure 5 shows the tissues from which the mRNAs corresponding to the 5′ ESTs in each of the above described categories were obtained.

In addition to categorizing the 5′ ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5′ ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail below.

In addition, 5′ ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5′ EST. By comparing mRNA expression patterns and quantities in

samples taken from healthy individuals with those from individuals suffering from a particular disease, 5′ ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5′ ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5′ ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

EXAMPLE 26

Evaluation of Expression Levels and Patterns of mRNAs

Corresponding to 5′ ESTs or Extended cDNAs

Expression levels and patterns of mRNAs corresponding to 5′ ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5′ EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5′ EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5′ ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain the 5′ or 3′ most region of the cleaved cDNA are isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs.

A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second

pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5′ ESTs or extended cDNAs to determine which 5′ ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5′ ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5′ ESTs or fragments of the full length cDNAs, extended cDNAs, or 5′ ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5′ ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (*Science* **270**:467-470, 1995; *Proc. Natl. Acad. Sci. U.S.A.* **93**:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5′ ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm^2 microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5′ ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5′ ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides. After hybridization and washing in controlled conditions, the hybridized mRNAs are

detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5′ ESTs or extended cDNAs can be done through high density nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al. (Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5′ ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., *supra*) or synthesized and then addressed to the chip (Sosnowski et al., *supra*). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., *supra* and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5′ EST or extended cDNA from which the oligonucleotide sequence has been designed.

III. Use of 5′ ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5′ ESTs which include the 5′ end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5′ ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5′ end of the corresponding mRNA for several secreted proteins.

The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5′ ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-84 and 130-154. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-84 and 130-154. In further embodiments, the extended cDNAs encode at least 30 amino amino acids of the sequences of SEQ ID NOs: 40-84 and 130-154. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-84 and 130-154.

EXAMPLE 27

General Method for Using 5′ ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5′ ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5′ EST in the NETGENE™ database, including those 5′ ESTs encoding secreted proteins. The method is summarized in Figure 6.

1. Obtaining Extended cDNAs

a) First strand synthesis

The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

b) Second strand synthesis

A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer

from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

c) Sequencing extended cDNAs

Sequencing of extended cDNAs can be performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product

size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls and validation steps are carried out as described in example 15.

3. Cloning of Full Length Extended cDNAs

The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

4. Computer Analysis of Full Length Extended cDNA

Sequences of all full length extended cDNAs may then be subjected to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S=72; identity=70%; and length = 40 nucleotides. Polyadenylation signal and polyA tail which were not search for the

5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last fifty nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W=6, S=10, E=1000, and identity=90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W=8 and B=10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not of interest are searched as follows.

a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminants sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungal contaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones

showing extensive homology to repeats , i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 85% or more than 30 nucleotides if the homology was at least 90%, were flagged.

b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it. The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

c) Identification of functional features

Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. **14**: 4683-4690 (1986)) and the modification described in Example 22.

d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences, EST sequences , patented sequences and recently identified sequences available at the time of filing the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in public databases using Swissprot, PIR and Genptept releases available

at the time of filing the priority documents for the present application. These analyses were performed using BLASTP with the parameter W=8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001. Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

As used herein the term "cDNA codes of SEQ ID NOs. 40-84 and 130-154" encompasses the nucleotide sequences of SEQ ID NOs. 40-84 and 130-154, fragments of SEQ ID NOs. 40-84 and 130-154, nucleotide sequences homologous to SEQ ID NOs. 40-84 and 130-154 or homologous to fragments of SEQ ID NOs. 40-84 and 130-154, and sequences complementary to all of the preceding sequences. The fragments include portions of SEQ ID NOs. 40-84 and 130-154 comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of SEQ ID NOs. 40-84 and 130-154. Preferably, the fragments are novel fragments. Homologous sequences and fragments of SEQ ID NOs. 40-84 and 130-154 refer to a sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, or 75% homology to these sequences. Homology may be determined using any of the computer programs and parameters described herein, including BLAST2N with the default parameters or with any modified parameters. Homologous sequences also include RNA sequences in which uridines replace the thymines in the cDNA codes of SEQ ID NOs. 40-84 and 130-154. The homologous sequences may be obtained using any of the procedures described herein or may result from the correction of a sequencing error as described above. It will be appreciated that the cDNA codes of SEQ ID NOs. 40-84 and 130-154 can be represented in the traditional single character format (See the inside back cover of Stamier, Lubert. *Biochemistry*, 3rd edition. W. H Freeman & Co., New York.) or in any other format which records the identity of the nucleotides in a sequence.

As used herein the term "polypeptide codes of SEQ ID NOS. 85-129 and 155-179" encompasses the polypeptide sequence of SEQ ID NOs. 85-129 and 155-179 which are encoded by the extended cDNAs of SEQ ID NOs. 40-84 and 130-154, polypeptide sequences homologous to the polypeptides of SEQ ID NOS. 85-129 and 155-179, or fragments of any of the preceding sequences. Homologous polypeptide sequences refer to a polypeptide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, 75% homology to one of the polypeptide sequences of SEQ ID NOS. 85-129 and 155-179. Homology may be determined using any of the computer programs and parameters described herein, including FASTA with the default parameters or with any modified parameters. The homologous sequences may be obtained using any of the procedures described herein or may result from the correction of a sequencing error as described above. The polypeptide fragments comprise at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of the polypeptides of SEQ ID NOS. 85-129 and 155-179. Preferably, the fragments are novel fragments. It will be appreciated that the polypeptide codes of the SEQ ID NOS. 85-129 and 155-179 can be represented in the traditional single character

format or three letter format (See the inside back cover of Starrier, Lubert. *Biochemistry*, 3rd edition. W. H Freeman & Co., New York.) or in any other format which relates the identity of the polypeptides in a sequence.

It will be appreciated by those skilled in the art that the cDNA codes of SEQ ID NOs. 40-84 and 130-154 and polypeptide codes of SEQ ID NOS. 85-129 and 155-179 can be stored, recorded, and manipulated on any medium which can be read and accessed by a computer. As used herein, the words "recorded" and "stored" refer to a process for storing information on a computer medium. A skilled artisan can readily adopt any of the presently known methods for recording information on a computer readable medium to generate manufactures comprising one or more of the cDNA codes of SEQ ID NOs. 40-84 and 130-154, one or more of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179. Another aspect of the present invention is a computer readable medium having recorded thereon at least 2, 5, 10, 15, 20, 25, 30, or 50 cDNA codes of SEQ ID NOs. 40-84 and 130-154. Another aspect of the present invention is a computer readable medium having recorded thereon at least 2, 5, 10, 15, 20, 25, 30, or 50 polypeptide codes of SEQ ID NOS. 85-129 and 155-179.

Computer readable media include magnetically readable media, optically readable media, electronically readable media and magnetic/optical media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, DVD, RAM, or ROM as well as other types of other media known to those skilled in the art.

Embodiments of the present invention include systems, particularly computer systems which contain the sequence information described herein. As used herein, "a computer system" refers to the hardware components, software components, and data storage components used to analyze the nucleotide sequences of the cDNA codes of SEQ ID NOs. 40-84 and 130-154, or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179. The computer system preferably includes the computer readable media described above, and a processor for accessing and manipulating the sequence data.

Preferably, the computer is a general purpose system that comprises a central processing unit (CPU), one or more data storage components for storing data, and one or more data retrieving devices for retrieving the data stored on the data storage components. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable.

In one particular embodiment, the computer system includes a processor connected to a bus which is connected to a main memory (preferably implemented as RAM) and one or more data storage devices, such as a hard drive and/or other computer readable media having data recorded thereon. In some embodiments, the computer system further includes one or more data retrieving devices for reading the data stored on the data storage components. The data retrieving device may represent, for example, a floppy disk drive, a compact disk drive, a magnetic tape drive, etc. In some embodiments, the data storage component is a removable computer readable medium such as a floppy disk, a compact disk, a magnetic tape, etc. containing control logic and/or data recorded thereon. The computer system may advantageously include or be programmed by appropriate software for reading the control logic and/or the data from the data storage component once inserted in the data retrieving device. Software for accessing and processing the nucleotide sequences of the cDNA codes of SEQ ID NOs. 40-

84 and 130-154, or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179 (such as search tools, compare tools, and modeling tools etc.) may reside in main memory during execution.

In some embodiments, the computer system may further comprise a sequence comparer for comparing the above-described cDNA codes of SEQ ID NOs. 40-84 and 130-154 or polypeptide codes of SEQ ID NOS. 85-129 and 155-179 stored on a computer readable medium to reference nucleotide or polypeptide sequences stored on a computer readable medium. A "sequence comparer" refers to one or more programs which are implemented on the computer system to compare a nucleotide or polypeptide sequence with other nucleotide or polypeptide sequences and/or compounds including but not limited to peptides, peptidomimetics, and chemicals stored within the data storage means. For example, the sequence comparer may compare the nucleotide sequences of the cDNA codes of SEQ ID NOs. 40-84 and 130-154, or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179 stored on a computer readable medium to reference sequences stored on a computer readable medium to identify homologies, motifs implicated in biological function, or structural motifs. The various sequence comparer programs identified elsewhere in this patent specification are particularly contemplated for use in this aspect of the invention.

Accordingly, one aspect of the present invention is a computer system comprising a processor, a data storage device having stored thereon a cDNA code of SEQ ID NOs. 40-84 and 130-154 or a polypeptide code of SEQ ID NOS. 85-129 and 155-179, a data storage device having retrievably stored thereon reference nucleotide sequences or polypeptide sequences to be compared to the cDNA code of SEQ ID NOs. 40-84 and 130-154 or polypeptide code of SEQ ID NOS. 85-129 and 155-179 and a sequence comparer for conducting the comparison. The sequence comparer may indicate a homology level between the sequences compared or identify structural motifs in the above described cDNA code of SEQ ID NOs. 40-84 and 130-154 and polypeptide codes of SEQ ID NOS. 85-129 and 155-179 or it may identify structural motifs in sequences which are compared to these cDNA codes and polypeptide codes. In some embodiments, the data storage device may have stored thereon the sequences of at least 2, 5, 10, 15, 20, 25, 30, or 50 of the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or polypeptide codes of SEQ ID NOS. 85-129 and 155-179.

Another aspect of the present invention is a method for determining the level of homology between a cDNA code of SEQ ID NOs. 40-84 and 130-154 and a reference nucleotide sequence, comprising the steps of reading the cDNA code and the reference nucleotide sequence through the use of a computer program which determines homology levels and determining homology between the cDNA code and the reference nucleotide sequence with the computer program. The computer program may be any of a number of computer programs for determining homology levels, including those specifically enumerated below, including BLAST2N with the default parameters or with any modified parameters. The method may be implemented using the computer systems described above. The method may also be performed by reading 2, 5, 10, 15, 20, 25, 30, or 50 of the above described cDNA codes of SEQ ID NOs. 40-84 and 130-154 through use of the computer program and determining homology between the cDNA codes and reference nucleotide sequences .

Alternatively, the computer program may be a computer program which compares the nucleotide sequences of the cDNA codes of the present invention, to reference nucleotide sequences in order to determine whether the cDNA code of SEQ ID NOs. 40-84 and 130-154 differs from a reference nucleic acid sequence at one or more positions. Optionally such a program records the length and identity of inserted, deleted or substituted nucleotides with respect to the sequence of either the reference polynucleotide or the cDNA code of SEQ ID NOs. 40-84 and 130-154. In one embodiment, the computer program may be a program which determines whether the nucleotide sequences of the cDNA codes of SEQ ID NOs. 40-84 and 130-154 contain a single nucleotide polymorphism (SNP) with respect to a reference nucleotide sequence. This single nucleotide polymorphism may comprise a single base substitution, insertion, or deletion.

Another aspect of the present invention is a method for determining the level of homology between a polypeptide code of SEQ ID NOS. 85-129 and 155-179 and a reference polypeptide sequence, comprising the steps of reading the polypeptide code of SEQ ID NOS. 85-129 and 155-179 and the reference polypeptide sequence through use of a computer program which determines homology levels and determining homology between the polypeptide code and the reference polypeptide sequence using the computer program.

Accordingly, another aspect of the present invention is a method for determining whether a cDNA code of SEQ ID NOs. 40-84 and 130-154 differs at one or more nucleotides from a reference nucleotide sequence comprising the steps of reading the cDNA code and the reference nucleotide sequence through use of a computer program which identifies differences between nucleic acid sequences and identifying differences between the cDNA code and the reference nucleotide sequence with the computer program. In some embodiments, the computer program is a program which identifies single nucleotide polymorphisms. The method may be implemented by the computer systems described above. The method may also be performed by reading at least 2, 5, 10, 15, 20, 25, 30, or 50 of the cDNA codes of SEQ ID NOs. 40-84 and 130-154 and the reference nucleotide sequences through the use of the computer program and identifying differences between the cDNA codes and the reference nucleotide sequences with the computer program.

In other embodiments the computer based system may further comprise an identifier for identifying features within the nucleotide sequences of the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179.

An "identifier" refers to one or more programs which identifies certain features within the above-described nucleotide sequences of the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179. In one embodiment, the identifier may comprise a program which identifies an open reading frame in the cDNAs codes of SEQ ID NOs. 40-84 and 130-154.

In another embodiment, the identifier may comprise a molecular modeling program which determines the 3-dimensional structure of the polypeptides codes of SEQ ID NOS. 85-129 and 155-179. In some embodiments, the molecular modeling program identifies target sequences that are most compatible with profiles representing the structural environments of the residues in known three-dimensional protein structures.

(See, e.g., Eisenberg et al., U.S. Patent No. 5,436,850 issued July 25, 1995). In another technique, the known three-dimensional structures of proteins in a given family are superimposed to define the structurally conserved regions in that family. This protein modeling technique also uses the known three-dimensional structure of a homologous protein to approximate the structure of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179. (See e.g., Srinivasan, et al., U.S. Patent No. 5,557,535 issued September 17, 1996). Conventional homology modeling techniques have been used routinely to build models of proteases and antibodies. (Sowdhamini et al., Protein Engineering 10:207, 215 (1997)). Comparative approaches can also be used to develop three-dimensional protein models when the protein of interest has poor sequence identity to template proteins. In some cases, proteins fold into similar three-dimensional structures despite having very weak sequence identities. For example, the three-dimensional structures of a number of helical cytokines fold in similar three-dimensional topology in spite of weak sequence homology.

The recent development of threading methods now enables the identification of likely folding patterns in a number of situations where the structural relatedness between target and template(s) is not detectable at the sequence level. Hybrid methods, in which fold recognition is performed using Multiple Sequence Threading (MST), structural equivalencies are deduced from the threading output using a distance geometry program DRAGON to construct a low resolution model, and a full-atom representation is constructed using a molecular modeling package such as QUANTA.

According to this 3-step approach, candidate templates are first identified by using the novel fold recognition algorithm MST, which is capable of performing simultaneous threading of multiple aligned sequences onto one or more 3-D structures. In a second step, the structural equivalencies obtained from the MST output are converted into interresidue distance restraints and fed into the distance geometry program DRAGON, together with auxiliary information obtained from secondary structure predictions. The program combines the restraints in an unbiased manner and rapidly generates a large number of low resolution model confirmations. In a third step, these low resolution model confirmations are converted into full-atom models and subjected to energy minimization using the molecular modeling package QUANTA. (See e.g., Aszódi et al., Proteins:Structure, Function, and Genetics, Supplement 1:38-42 (1997)).

The results of the molecular modeling analysis may then be used in rational drug design techniques to identify agents which modulate the activity of the polypeptide codes of SEQ ID NOS. 85-129 and 155-179.

Accordingly, another aspect of the present invention is a method of identifying a feature within the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the polypeptide codes of SEQ ID NOS. 85-129 and 155-179 comprising reading the cDNA code(s) or the polypeptide code(s) through the use of a computer program which identifies features therein and identifying features within the cDNA code(s) or polypeptide code(s) with the computer program. In one embodiment, computer program comprises a computer program which identifies open reading frames. In a further embodiment, the computer program identifies structural motifs in a polypeptide sequence. In another embodiment, the computer program comprises a molecular modeling program. The method may be performed by reading a single sequence or at least 2, 5, 10, 15, 20, 25, 30, or 50

of the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the polypeptide codes of SEQ ID NOS. 85-129 and 155-179 through the use of the computer program and identifying features withing the cDNA codes or polypeptide codes with the computer program.

The cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the polypeptide codes of SEQ ID NOS. 85-129 and 155-179 may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the polypeptide codes of SEQ ID NOS. 85-129 and 155-179 may be stored as text in a word processing file, such as MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE. In addition, many computer programs and databases may be used as sequence comparers, identifiers, or sources of reference nucleotide or polypeptide sequences to be compared to the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the polypeptide codes of SEQ ID NOS. 85-129 and 155-179. The following list is intended not to limit the invention but to provide guidance to programs and databases which are useful with the cDNA codes of SEQ ID NOs. 40-84 and 130-154 or the polypeptide codes of SEQ ID NOS. 85-129 and 155-179. The programs and databases which may be used include, but are not limited to: MacPattern (EMBL), DiscoveryBase (Molecular Applications Group), GeneMine (Molecular Applications Group), Look (Molecular Applications Group), MacLook (Molecular Applications Group), BLAST and BLAST2 (NCBI), BLASTN and BLASTX (Altschul et al, *J. Mol. Biol.* 215: 403 (1990)), FASTA (Pearson and Lipman, *Proc. Natl. Acad. Sci. USA*, 85: 2444 (1988)), FASTDB (Brutlag et al. Comp. App. Biosci. 6:237-245, 1990), Catalyst (Molecular Simulations Inc.), Catalyst/SHAPE (Molecular Simulations Inc.), Cerius^2.DBAccess (Molecular Simulations Inc.), HypoGen (Molecular Simulations Inc.), Insight II, (Molecular Simulations Inc.), Discover (Molecular Simulations Inc.), CHARMm (Molecular Simulations Inc.), Felix (Molecular Simulations Inc.), DelPhi, (Molecular Simulations Inc.), QuanteMM, (Molecular Simulations Inc.), Homology (Molecular Simulations Inc.), Modeler (Molecular Simulations Inc.), ISIS (Molecular Simulations Inc.), Quanta/Protein Design (Molecular Simulations Inc.), WebLab (Molecular Simulations Inc.), WebLab Diversity Explorer (Molecular Simulations Inc.), Gene Explorer (Molecular Simulations Inc.), SeqFold (Molecular Simulations Inc.), the EMBL/Swissprotein database, the MDL Available Chemicals Directory database, the MDL Drug Data Report data base, the Comprehensive Medicinal Chemistry database, Derwents's World Drug Index database, the BioByteMasterFile database, the Genbank database, and the Genseqn database. Many other programs and data bases would be apparent to one of skill in the art given the present disclosure.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn-helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

5. <u>Selection of Cloned Full Length Sequences of the Present Invention</u>

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the ORF, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

b) Manual sequence selection

Manual selection can be carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedure, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then,

homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

EXAMPLE 28

Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO: 19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21. This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5′ ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5′ ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID NOs: 40-84 and 130-154. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-84 and 130-154 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in

Table IV), the locations of the nucleotides in SEQ ID NOs: 40-84 and 130-154 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-84 and 130-154 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-84 and 130-154 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-84 and 130-154 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at http://expasy.hcuge.ch/sprot/prosite.html. Prosite_convert and prosite_scan programs (http://ulrec3.unil.ch/ftpserveur/prosite_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native proteins) was skipped during the search with prosite_scan. The program used to shuffle protein sequences (db_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite_statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite_scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 85-129 and 155-179, the locations of the amino acid residues of SEQ ID NOs: 85-129 and 155-179 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 85-129 and 155-179 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 85-129 and 155-179 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-84 and 130-154 and the amino acid sequences encoded by SEQ ID NOs: 40-84 and 130-154 (i.e. amino acid sequences of SEQ ID NOs: 85-129 and 155-179) are provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-84 and 130-154 can readily be screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing such errors or ambiguities on both strands. Sequences containing such errors will generally be at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% homologous to the sequences of SEQ ID Nos. 85-129 and 155-179 and such sequences are included in the nucleic acids and polypeptides of the present invention. Nucleic acid fragments for resolving sequencing errors or ambiguities may be obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any

such ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences encoded by the DNA containing the error or ambiguity. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-84 and 130-154) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-84), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA, U.S.A., 20110-2209. Each extended cDNA clone has been transfected into separate bacterial cells (E-coli) for this composite deposit. Table VI lists the deposit numbers of the clones of SEQ ID Nos: 40-84. A pool of cells designated SignalTag 28011999, which contains the clones of SEQ ID NOs 71-84 was mailed to the European Collection of Cell Cultures, (ECACC) Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom on January 28, 1999 and was received on January 29, 1999. This pool of cells has the ECACC Accession # XXXXXX. One or more pools of cells containing the extended cDNAs of SEQ ID Nos: 130-154, from which the cells containing a particular polynucleotide is obtainable, will be deposited with the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom and will be assigned ECACC deposit number XXXXXXX. Table VII provides the internal designation number assigned to each SEQ ID NO. and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a NotI, PstI double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) Preferably, the probe is designed to have a T_m of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with (-[^{32}P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately $4X10^6$ dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to $1X10^6$ dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence

ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5′ ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5′ ESTs. Example 29 below provides an example of such methods.

EXAMPLE 29

Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5′ ESTs

5'ESTs or extended cDNAs of the present invention may also be used to isolate extended cDNAs or nucleic acids homologous to extended cDNAs from a cDNA library or a genomic DNA library. Such cDNA library or genomic DNA library may be obtained from a commercial source or made using other techniques familiar to those skilled in the art. One example of such cDNA library construction is as follows.

PolyA+ RNAs are prepared and their quality checked as described in Example 13. Then, polyA+ RNAs are ligated to an oligonucleotide tag using either the chemical or enzymatic methods described in above sections 1 and 2. In both cases, the oligonucleotide tag may contain a restriction site such as Eco RI to facilitate further subcloning procedures. Northern blotting is then performed to check the size of ligatured mRNAs and to ensure that the mRNAs were actually tagged.

As described in Example 14, first strand synthesis is subsequently carried out for mRNAs joined to the oligonucleotide tag replacing the random nonamers by an oligodT primer. For instance, this oligodT primer may contain an internal tag of 4 nucleotides which is different from one tissue to the other. Alternatively, the oligonucleotide of SEQ ID NO:14 may be used. Following second strand synthesis using a primer contained in the oligonucleotide tag attached to the 5' end of mRNA, the blunt ends of the obtained double stranded full length DNAs are modified into cohesive ends to allow subcloning into the Eco RI and Hind III sites of a Bluescript vector using the addition of a Hind III adaptor to the 3' end of full length DNAs.

The extended full length DNAs are then separated into several fractions according to their sizes using techniques familiar to those skilled in the art. For example, electrophoretic separation may be applied in order to yield 3 or 6 different fractions. Following gel extraction and purification, the DNA fractions are subcloned into Bluescript vectors, transformed into competent bacteria and propagated under appropriate antibiotic conditions.

Such full length cDNA libraries may then be sequenced as follows or used in screening procedures to obtain nucleic acids homologous to extended cDNAs or 5' ESTs as described below.

The 5' end of extended cDNA isolated from the full length cDNA libraries or of nucleic acid homologous thereto may then be sequenced as described in example 27. In a first step, the sequence corresponding to the 5' end of the mRNA is obtained; If this sequence either corresponds to a SignalTag™ 5'EST or fulfills the criteria to be one, the cloned insert is subcloned into an appropriate vector such as pED6dpc2, double-sequenced and submitted to the analysis and selection procedures described in Example 27.

Such cDNA or genomic DNA librairies may be used to isolate extended cDNAs obtained from 5′ EST or nucleic acids homologous to extended cDNAs or 5′ EST as follows. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5′ EST or extended cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5′ EST or extended cDNA. More preferably, the probe comprises at least 20 to 30 consecutive nucleotides from the 5′ EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 conscutive nucleotides from the 5′ EST or extended cDNA. Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook *et al., Molecular Cloning: A Laboratory Manual 2d Ed.*, Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5′ EST or extended cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5′ EST or extended cDNA. More preferably, the probe comprises 20 to 30 consecutive nucleotides from the 5′ EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 conscutive nucleotides from the 5′ EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, *in vitro* transcription, and non radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After blocking of non specific sites, the filter is incubated with the labeled probe for an amount of time sufficient to allow binding of the probe to cDNAs or genomic DNAs containing a sequence capable of hybridizing thereto.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated as described below.

1. Identification of Extended cDNA or Genomic DNA Sequences Having a High Degree of Homology to the Labeled Probe

To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100 µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100 µg denatured fragmented

salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook *et al.*, *supra*.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions.

Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5′ ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

2. Obtaining Extended cDNA or Genomic DNA Sequences Having Lower Degrees of Homology to the Labeled Probe

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a sodium concentration of approximately 1M. Following hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

3. Determination of the Degree of Homology between the Obtained Extended cDNAs or Genomic DNAs and the Labeled Probe

To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. The sequences of the extended cDNA or 5'EST and the homologous sequences may be stored on a computer readable medium as described in Example 17 above and may be compared using any of a variety of algorithms familiar to those skilled in the art. For example, if it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be determined using algorithms such as BLAST2N; parameters may be adapted depending on the sequence length and degree of homology studied. For example, the default parameters or the parameters in Table I and II may be used to determine homology levels. Alternatively, the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived may be determined using the FASTDB algorithm described in Brutlag et al. Comp. App. Biosci. 6:237-245, 1990. In such analyses the parameters may be selected as follows: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the sequence which hybridizes to the probe, whichever is shorter. Because the FASTDB program does not consider 5' or 3' truncations when calculating homology levels, if the sequence which hybridizes to the probe is truncated relative to the sequence of the extended cDNA or 5'EST from which the probe was derived the homology level is manually adjusted by calculating the number of nucleotides of the extended cDNA or 5'EST which are not matched or aligned with the hybridizing sequence, determining the percentage of total nucleotides of the hybridizing sequence which the non-matched or non-aligned nucleotides represent, and subtracting this percentage from the homology level. For example, if the hybridizing sequence is 700 nucleotides in length and the extended cDNA sequence is 1000 nucleotides in length wherein the first 300 bases at the 5' end of the extended cDNA are absent from the hybridizing sequence, and wherein the overlapping 700 nucleotides are identical, the homology level would be adjusted as follows. The non-matched, non-aligned 300 bases represent 30% of the length of the extended cDNA. If the overlapping 700 nucleotides are 100% identical, the adjusted homology level would be 100-30=70% homology. It should be noted that the preceding adjustments are only made when the non-matched or non-aligned nucleotides are at the 5' or 3' ends. No adjustments are made if the non-matched or non-aligned sequences are internal or under any other conditions.

For example, using the above methods, nucleic acids having at least 95% nucleic acid homology, at least 96% nucleic acid homology, at least 97% nuleic acid homology, at least 98% nucleic acid homology, at least 99% nucleic acid homology, or more than 99% nucleic acid homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Such nucleic acids may be allelic variants or related nucleic

acids from other species. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. The sequences encoded by the extended cDNA or 5'EST and the sequences encoded by the homologous sequences may be stored on a computer readable medium as described in Example 17 above and may be compared using any of a variety of algorithms familiar to those skilled in the art. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied, for example the default parameters or the parameters in Table I and II, one can obtain nucleic acids encoding proteins having at least 99%, at least 98%, at least 97%, at least 96%, at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. In some embodiments, the homology levels can be determined using the "default" opening penalty and the "default" gap penalty, and a scoring matrix such as PAM 250 (a standard scoring matrix; see Dayhoff et al., in: Atlas of Protein Sequence and Structure, Vol. 5, Supp. 3 (1978)).

Alternatively, the level of homology may be determined using the FASTDB algorithm described by Brutlag et al. Comp. App. Biosci. 6:237-245, 1990. In such analyses the parameters may be selected as follows: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=Sequence Length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the homologous sequence, whichever is shorter. If the homologous amino acid sequence is shorter than the amino acid sequence encoded by the extended cDNA or 5'EST as a result of an N terminal and/or C terminal deletion the results may be manually corrected as follows. First, the number of amino acid residues of the amino acid sequence encoded by the extended cDNA or 5'EST which are not matched or aligned with the homologous sequence is determined. Then, the percentage of the length of the sequence encoded by the extended cDNA or 5'EST which the non-matched or non-aligned amino acids represent is calculated. This percentage is subtracted from the homology level. For example wherein the amino acid sequence encoded by the extended cDNA or 5'EST is 100 amino acids in length and the length of the homologous sequence is 80 amino acids and wherein the amino acid sequence encoded by the extended cDNA or 5'EST is truncated at the N terminal end with respect to the homologous sequence, the homology level is calculated as follows. In the preceding scenario there are 20 non-matched, non-aligned amino acids in the sequence encoded by the extended cDNA or 5'EST. This represents 20% of the length of the amino acid sequence encoded by the extended cDNA or 5'EST. If the remaining amino

acids are 1005 identical between the two sequences, the homology level would be 100%-20%=80% homology. No adjustments are made if the non-matched or non-aligned sequences are internal or under any other conditions.

In addition to the above described methods, other protocols are available to obtain extended cDNAs using 5' ESTs as outlined in the following paragraphs.

Extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing polyA selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the polyA tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20 to 30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RT-PCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by hybridizing an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20 to 30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described *In Current Protocols in Molecular Biology*, John Wiley 503 Sons, Inc. 1997 and Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, other procedures may be used for obtaining full length cDNAs or extended cDNAs. In one approach, full length or extended cDNAs are prepared from mRNA and cloned into double stranded phagemids as follows. The cDNA library in the double stranded phagemids is then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and an exonuclease (Chang *et al.*, *Gene* 127:95-8, 1993). A biotinylated oligonucleotide comprising the sequence of a 5′ EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5′ EST. More preferably, the fragment comprises 20-30 consecutive nucleotides from the 5′ EST. In some procedures, the fragment may comprise at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 conscutive nucleotides from the 5′ EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5′ EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet (Fry *et al.*, *Biotechniques*, 13: 124-131, 1992). Therafter, the resulting phagemids containing the 5′ EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5′ EST sequence. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5′ EST sequence are identified by colony PCR or colony hybridization.

Using any of the above described methods in section III, a plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved off may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5′ ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

EXAMPLE 30

Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-84 and 130-154 listed in Table IV and in the accompanying sequence listing.

Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-84 and 130-154 as defined in Table IV above.

It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-84 and 130-154. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-84 and 130-154 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEQ ID NOs: 40-84 and 130-154 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-84 and 130-154. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-84 and 130-154 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 85-129 and 155-179 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEQ ID NOs. 85-129 and 155-179 or the nucleic acids encoding the biologically active form of the polypeptides differ from

those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEQ ID NOs. 85-129 and 155-179 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 40-84 and 130-154 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-84 and 130-154 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID NOs. 40-84 and 130-154. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40-84 and 130-154 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID NOs. 85-129 and 155-179 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 85-129 and 155-179. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 85-129 and 155-179. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 85-129 and 155-179. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 85-129 and 155-179.

The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression

systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5′ ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using BglI and SalI restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the *gag* gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5′primer and BglII at the 5′ end of the corresponding cDNA 3′ primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with PstI, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5′ EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5′ EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5′ EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the

polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al., (**Basic Methods in Molecular Biology**, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro Express™ Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5′ ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

EXAMPLE 31

Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface

The proteins encoded by the 5′ ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: **Current Protocols in Immunology**, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. **J. Immunol.** 137:3494-3500, 1986. Bertagnolli et al. **J. Immunol.** 145:1706-1712, 1990. Bertagnolli et al., **Cellular Immunology** 133:327-341, 1991. Bertagnolli, et al. **J. Immunol.** 149:3778-3783, 1992; Bowman et al., **J. Immunol.** 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells and thymocytes are known. These include the techniques disclosed in **Current Protocols in Immunology**. J.E. Coligan et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. **Current Protocols in Immunology.**, *supra* Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, **Current Protocols in Immunology.**, J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., **J. Exp. Med.** 173:1205-1211, 1991; Moreau et al., **Nature** 36:690-692, 1988; Greenberger et al., **Proc. Natl. Acad. Sci. U.S.A.** 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 **Current Protocols in Immunology.** J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., **Proc. Natl. Acad. Sci. U.S.A.** 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 **Current Protocols in Immunology**. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 **Current Protocols in Immunology**. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., **Proc. Natl. Acad. Sci. USA** 77:6091-6095, 1980; Weinberger et al., **Eur. J. Immun.** 11:405-411, 1981; Takai et al., **J. Immunol.** 137:3494-3500, 1986; Takai et al., **J. Immunol.** 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 33

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., **Proc. Natl. Acad. Sci. USA** 78:2488-2492, 1981; Herrmann et al., **J. Immunol.** 128:1968-1974, 1982; Handa et al., **J. Immunol.** 135:1564-1572, 1985; Takai et al., **J. Immunol.** 137:3494-3500, 1986; Takai et al., **J. Immunol.** 140:508-512, 1988; Herrmann et al., **Proc. Natl. Acad. Sci. USA** 78:2488-2492, 1981; Herrmann et al., **J. Immunol.** 128:1968-1974, 1982; Handa et al., **J. Immunol.** 135:1564-1572, 1985; Takai et al., **J. Immunol.** 137:3494-3500, 1986; Bowman et al., **J. Virology** 61:1992-1998; Takai et al., **J. Immunol.** 140:508-512, 1988; Bertagnolli et al., **Cellular Immunology** 133:327-341, 1991; Brown et al., **J. Immunol.** 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, **J. Immunol.** 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in **Current Protocols in Immunology**. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., **J. Immunol.** 137:3494-3500, 1986; Takai et al.; **J. Immunol.** 140:508-512, 1988; Bertagnolli et al., **J. Immunol.** 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., **J. Immunol.** 134:536-544, 1995; Inaba et al., **Journal of Experimental Medicine** 173:549-559, 1991; Macatonia et al., **Journal of Immunology** 154:5071-5079, 1995;

Porgador et al., **Journal of Experimental Medicine** 182:255-260, 1995; Nair et al., **Journal of Virology** 67:4062-4069, 1993; Huang et al., **Science** 264:961-965, 1994; Macatonia et al., **Journal of Experimental Medicine** 169:1255-1264, 1989; Bhardwaj et al., **Journal of Clinical Investigation** 94:797-807, 1994; and Inaba et al., **Journal of Experimental Medicine** 172:631-640, 1990.

The proteins encoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., **Cytometry** 13:795-808, 1992; Gorczyca et al., **Leukemia** 7:659-670, 1993; Gorczyca et al., **Cancer Research** 53:1945-1951, 1993; Itoh et al., **Cell** 66:233-243, 1991; Zacharchuk, **Journal of Immunology** 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., **International Journal of Oncology** 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell

responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of

autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory form of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the

invariant chain,can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 34

Assaying the Proteins Expressed from Extended cDNAsor Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. **Cellular Biology** 15:141-151, 1995; Keller et al., **Molecular and Cellular Biology** 13:473-486, 1993; McClanahan et al., **Blood** 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in **Culture of Hematopoietic Cells**. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., **Proc. Natl. Acad. Sci. USA** 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in **Culture of Hematopoietic Cells**. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., **Experimental Hematology** 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In **Culture of Hematopoietic Cells**. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in **Culture of Hematopoietic Cells**. R.I. Freshney, et al. Eds. pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in **Culture of Hematopoietic Cells**. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and

proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 35

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. WO95/16035, International Patent Publication No. WO95/05846 and International Patent Publication No. WO91/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage

repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 36

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., **Endocrinology** 91:562-572, 1972; Ling et al., **Nature** 321:779-782, 1986; Vale et al., **Nature** 321:776-779, 1986; Mason et al., **Nature** 318:659-663, 1985; Forage et al., **Proc. Natl. Acad. Sci. USA** 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) **Current Protocols in Immunology**, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience ; Taub et al. **J. Clin. Invest.** 95:1370-1376, 1995; Lind et al. **APMIS** 103:140-146, 1995; Muller et al. **Eur. J. Immunol.** 25:1744-1748; Gruber et al. **J. of Immunol.** 152:5860-5867, 1994; Johnston et al. **J. of Immunol.** 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 36A

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

EXAMPLE 37

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., **J. Clin. Pharmacol.** 26:131-140, 1986; Burdick et al., **Thrombosis Res.** 45:413-419, 1987; Humphrey et al., **Fibrinolysis** 5:71-79 (1991); Schaub, **Prostaglandins** 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as,for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 38

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., **Proc. Natl. Acad. Sci. USA** 84:6864-6868, 1987; Bierer et al., **J. Exp. Med.** 168:1145-1156, 1988; Rosenstein et al., **J. Exp. Med.** 169:149-160, 1989; Stoltenborg et al., **J. Immunol. Methods** 175:59-68, 1994; Stitt et al., **Cell** 80:661-670, 1995; Gyuris et al., *Cell* 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

EXAMPLE 38A

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by

inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)),ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

EXAMPLE 38B

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

EXAMPLE 39

Identification of Proteins which Interact with
Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, *in vitro* transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives *in vitro* transcription. The resulting pools of mRNAs are introduced into *Xenopus laevis* oocytes. The oocytes are then assayed for a desired acitivity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase. A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry,

246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or chemical libraries,or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997).

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and translated *in vitro* and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may be capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs: 40-59, 61-73, 75, 77-82, and 130-154, a mature protein encoded by one of the sequences of SEQ ID NOs. 40-59, 61-75, 77-82, and 130-154, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-59, 61-73, 75-82, 84 and 130-154. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 85-129 and 155-179. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 85-129 and 155-179. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs:

85-129 and 155-179. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 85-129 and 155-179.

EXAMPLE 40

Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., **Nature 256**:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., **Meth. Enzymol. 70**:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. **Basic Methods in Molecular Biology** Elsevier, New York. Section 21-2.

B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. **J. Clin. Endocrinol. Metab. 33**:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: **Handbook of Experimental**

Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: **Manual of Clinical Immunology**, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

EXAMPLE 41

Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

EXAMPLE 42

Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive

labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5′ ESTs (or genomic DNAs obtainable therefrom).

EXAMPLE 43

Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

EXAMPLE 44

Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used.

These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

EXAMPLE 45

Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (**Basic Methods in Molecular Biology**, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., supra). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

EXAMPLE 46

Dot Blot Identification Procedure

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P^{32} using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and hybridized with labeled probe using techniques known in the art (Davis et al. supra). The ^{32}P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., **Proc. Natl. Acad. Sci. USA 82(6)**:1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

EXAMPLE 47

Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and XbaI. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P^{32}. The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species from which a sample is derived as described above.

EXAMPLE 48

Identification of Tissue Types or Cell Species by Means of Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semi-qualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ion-exchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous antisera is suitable for either procedure.

A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: **Basic 503 Clinical Immunology**, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: **Methods in Immunodiagnosis**, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example ^{125}I, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 μm, unfixed) of the unknown tissue and

known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: **Basic Methods in Molecular Biology** (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to55 µl, and containing from about 1 to 100 µg protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the

primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

EXAMPLE 49

Radiation hybrid mapping of Extended cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* **4**:509-517, 1989) and Cox et al., (*Science* **250**:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* **274**:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thymidine kinase (TK) (Foster et al., *Genomics* **33**:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* **4**:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* **29**:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* **14**:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* **11**:701-708, 1991).

EXAMPLE 50

Mapping of Extended cDNAs to Human

Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., **PCR Technology; Principles and Applications for DNA Amplification**. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 μCu of a ^{32}P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., **Genomics 6**:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

EXAMPLE 51

Mapping of Extended 5′ ESTs to Chromosomes

Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. (*Proc. Natl. Acad. Sci. U.S.A.*, **87**:6639-6643, 1990). Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 μM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 μg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCl (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100 μg/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at 70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM $CaCl_2$) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., *supra.*). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

EXAMPLE 52

Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. **Genome Research** 7:210-222, March 1997.

Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms chromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

EXAMPLE 53

Identification of genes associated with hereditary diseases or drug response

This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, **Mendelian Inheritance in Man** (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

VI. **Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors**

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such

secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

EXAMPLE 54

Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-59, 61-73, 75-82, 84, and 130-154 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5′ ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5′ ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5′ ESTs.

EXAMPLE 55

Use of Extended cDNAs or 5′ ESTs to Clone Upstream Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5′ ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer should be selected to be specific for the extended cDNA or 5′ EST of interest and should have a melting temperature, length, and location in the extended cDNA or ′ EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 µl of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 µM each of outer adaptor primer and outer gene specific primer, 1.1 mM of $Mg(OAc)_2$, and 1 µl of the Tth polymerase 50X mix in a total volume of 50 µl. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 µl of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 µl volume having a composition identical to that of the first PCR reaction except the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker™ kit. The second nested primer is specific for the particular extended cDNA or 5′ EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the

extended cDNA or 5′ EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C.

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5′ EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5′ EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5′ EST or extended cDNA sequences are identified by colony PCR or colony hybridization.

Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5′ ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

EXAMPLE 56

Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5′ ESTs are cloned into a suitable promoter reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, β galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5′ ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5′ EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

EXAMPLE 57

Cloning and Identification of Promoters

Using the method described in Example 55 above with 5′ ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5′ tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5′ postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5′ EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5′ EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5′ ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5′ EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

EXAMPLE 58

Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit avalilabe from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable

marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

EXAMPLE 59

Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., **Ann. Rev. Biochem. 55**:569-597 (1986) and Izant and Weintraub, **Cell 36**:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., **Pharmacol. Ther. 50(2)**:245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT WO94/23026 are used. In these moleucles, the 3′ end or both the 3′ and 5′ ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141 are used.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between $1x10^{-10}$M to $1x10^{-4}$M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of $1x10^{-7}$ translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., *supra*.

In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

EXAMPLE 60

Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target gene in cells which have been treated with the oligonucleotide . The cell functions to be monitored are predicted based upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived with known gene sequences that have been associated with a particular function. The cell functions can also be predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3′ end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (**Science 245**:967-971 (1989)).

EXAMPLE 61

Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be

introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

EXAMPLE 62

Use Of Signal Peptides Encoded By 5' Ests Or Sequences Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-called cargo, into tissue culture cells (Lin *et al., J. Biol. Chem.*, **270**: 14225-14258 (1995); Du *et al., J. Peptide Res.*, **51**: 235-243 (1998); Rojas *et al., Nature Biotech.*, **16**: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin *et al., supra*; Lin *et al., J. Biol. Chem.*, **271**: 5305-5308 (1996); Rojas *et al., J. Biol. Chem.*, **271**: 27456-27461 (1996); Liu *et al., Proc. Natl. Acad. Sci. USA*, **93**: 11819-11824 (1996); Rojas *et al., Bioch. Biophys. Res. Commun.*, **234**: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

EXAMPLE 63

Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequence presented in SEQ ID NO: 84 is apparently unlikely to be genuine full length cDNAs. This clone is more probably a 3' truncated cDNA sequence based on homology studies with existing protein sequences. Similarly, the sequences presented in SEQ ID NOs: 60, 76, 83 and 84 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although these sequences encode a potential start methionine, except for SEQ ID NO:60, they could represent a 5' truncated cDNA.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEQ ID NOs: 60, 74 and 83 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-84 and 130-154 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-84 and 130-154 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-84 and 130-154 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-84 and 130-154 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-84 and 130-154 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 85-129 and 155-179, the locations of the amino acid residues of SEQ ID NOs: 85-129 and 155-179 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 85-129 and 155-179 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 85-129 and 155-179 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

Example 64

Functional Analysis of Predicted Protein Sequences

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases : Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 53) and Swissprot (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 80% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (30 to 80% over the whole protein) indicating that the protein of the present invention is susceptible to have a function similar to the one of the matched protein.

The third category contains proteins exhibiting either high homology (90 to 100%) to a short domain or more remote homology (40 to 60%) to a larger domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 12, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition, all of the corrected amino acid sequences (SEQ ID NOs: 85-129 and 155-179) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package. Functional signatures and their locations are indicated in Table VIII.

A) Proteins which are closely related to known proteins

Protein of SEQ ID NO: 120 (internal designation 26-44-1-B5-CL3_1)

The protein of SEQ ID NO: 120 encoded by the extended cDNA SEQ ID NO: 75 isolated from ovary shows extensive homology to a human protein called phospholemman or PLM and its homologues in rodent and canine species. PLM is encoded by the nucleic acid sequence of Genbank accession number U72245 and has the amino acid sequence of SEQ ID NO : 180. Phospholemman is a prominent plasma membrane protein whose phosphorylation correlates with an increase in contractility of myocardium and skeletal muscle. Initially described as a simple chloride channel, it has recently been shown to be a channel for taurine that acts as an osmolyte in the regulation of cell volume (Moorman *et al, Adv Exp. Med. Biol.*, **442**:219-228 (1998)).

As shown by the alignment in Figure 10 between tha protein of SEQ ID NO:120 and PLM, the amino acid residues are identical except for positions 3 and 5 in the 92 amino acid long matched protein. The substitution of a proline residue at position 3 par another neutral residue, serine, is conservative. In addition, the protein of the invention also exhibits the typical ATP1G /PLM/MAT8 PROSITE signature (position 27 to 40 in bold in Figure 10) for a family containing mostly proteins known to be either chloride channels or chloride channel regulators In addition, the protein of invention contains 2 short transmembrane segments from positions 1 to 21 and from 37 to 57 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10** :685-686 (1994)). The first segment (in italic) corresponds to the signal peptide of PLM and

the second transmembrane domains (underlined) matches the transmembrane region (double-underlined) shown to be the chloride channel itself (Chen *et al., Circ. Res.*, **82**:367-374 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 120 may be involved in the regulation of cell volume and in tissue contractility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, diarrhea, fertility disorders, and in contractility disorders including muscle disorders, pulmonary disorders and myocardial disorders.

Proteins of SEQ ID NOs: 121 (internal designation 47-4-4-C6-CL2_3)

The protein of SEQ ID NO: 121 encoded by the extended cDNA SEQ ID NO: 76 found in substantia nigra shows extensive homology with the human E25 protein. The E25 protein is encoded by the nucleic acid sequence of Genbank accession number AF038953 and has the amino acid sequence of SEQ ID NO: 181. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells. In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder *et al, J. Biol. Chem.*, 271 :19475-19482 (1996)).

As shown by the alignments in Figure 11 between the protein of SEQ ID NO:121 and E25, the amino acid residues are identical except for positions 9, 24 and 121 in the 263 amino acid long matched sequence. All these substitutions are conservative. In addition, the protein of invention contains one short transmembrane segment from positions 1 to 21 (underlined in Figure 11) matching the one predicted for the murine E25 protein as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10** :685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 121 may be involved in cellular proliferation and differentiation, and/or in haematopoiesis. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hematological, chondro-osteogenic and embryogenetic disorders.

Proteins of SEQ ID NO: 128 (internal designation 58-34-2-H8-CL1_3)

The protein of SEQ ID NO: 128 encoded by the extended cDNA SEQ ID NO: 83 isolated from kidney shows extensive homology to the murine WW-domain binding protein 1 or WWBP-1. WWBP-1 is encoded by the nucleic acid sequence of Genbank accession number U40825 and has the amino acid sequence of SEQ ID NO: 182. This protein is expressed in placenta, lung, liver and kidney is thought to play a role in intracellular signaling by binding to the WW domain of the Yes protooncogene-associated protein via its so-called PY domain (Chen and Sudol, *Proc. Natl. Acad. Sci.*, **92** :7819-7823 (1995)). The WW – PY domains are thought to represent a new set of modular protein-binding sequences just like the SH3 – PXXP domains (Sudol *et al., FEBS Lett.*, **369** :67-71 (1995)).

As shown by the alignments of Figure 12 between the protein of SEQ ID NO:128 and WWBP-1, the amino acid residues are identical to those of the 305 amino acid long matched protein except for positions 53, 66, 78, 89, 92, 94, 96, 100, 102, 106, 110, 113, 124, 128, 136, 139, 140, 142-144, 166, 168, 173, 176, 178, 181, 182, 188, 196, 199, 201, 202, 207 and 210 of the matched protein. 68% of these substitutions are

conservative. Indeed the histidine-rich PY domain is present in the protein of the invention (positions 82-86 in bold in Figure 12).

Taken together, these data suggest that the protein of SEQ ID NO: 128 may play a role in intracellular signaling. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

B) Proteins which are remotely related to proteins with known functions

Protein of SEQ ID NO: 97 (internal designation 108-004-5-0-G6-FL)

The protein SEQ ID N°: 97 found in liver encoded by the extended cDNA SEQ ID NO: 52 shows homology to a lectin-like oxidized LDL receptor (LOX-1) found in human, bovine and murine species. Such type II proteins with a C-lectin-like domain, expressed in vascular endothelium and vascular-rich organs, bind and internalize oxidatively modified low-density lipoproteins (Sawamura *et al*, *Nature*, **386**:73-77, (1997)). The oxidized lipoproteins have been implicated in the pathogenesis of atherosclerosis, a leading cause of death in industrialized countries (see review by Parthasarathy *et al*, *Biochem. Pharmacol.* **56**:279-284 (1998)). In addition, type II membrane proteins with a C-terminus C-type lectin domain, also known as carbohydrate-recognition domains, also include proteins involved in target-cell recognition and cell activation.

The protein of invention has the typical structure of a type II protein belonging to the C-type lectin family. Indeed, it contains a short 31-amino-acid-long N-terminal tail, a transmembrane segment from positions 32 to 52 matching the one predicted for human LOX-1 and a large 177-amino-acid-long C-terminal tail as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10**:685-686 (1994)). All six cysteines of LOX-1 C-type lectin domain are also conserved in the protein of the invention (positions 102, 113, 130, 195, 208 and 216) although the characteristic PROSITE signature of this family is not. The LOX-1 protein is encoded by the nucleic acid sequence of Genbank accession number: AB010710.

Taken together, these data suggest that the protein of SEQ ID NO: 97 may be involved in the metabolism of lipids and/or in cell-cell or cell-matrix interactions and/or in cell activation. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, hyperlipidaemia, cardiovascular disorders and neurodegenerative disorders.

Protein of SEQ ID NO: 111 (internal designation 108-008-5-0-G12-FL)

The protein SEQ ID NO: 111 encoded by the extended cDNA SEQ ID NO:66 shows homology to a mitochondrial protein found in *Saccharomyces Cerevisiae* (PIR:S72254) which is similar to *E. Coli* ribosomal protein L36. The typical PROSITE signature for ribosomal L36 is present in the protein of the invention (positions 76-102) except for a substitution of a tryptophane residue instead of a valine, leucine, isoleucine, methionine or asparagine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 111 may be involved in protein biosynthesis. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer.

Protein of SEQ ID NO: 94 (internal designation 108-004-5-0-D10-FL)

The protein SEQ ID NO: 94 encoded by the extended cDNA SEQ ID NO: 49 shows remote homology to a subfamily of beta4-galactosyltransferases widely conserved in animals (human, rodents, cow and chicken). Such enzymes, usually type II membrane proteins located in the endoplasmic reticulum or in the Golgi apparatus, catalyzes the biosynthesis of glycoproteins, glycolipid glycans and lactose. Their characteristic features defined as those of subfamily A in Breton *et al, J. Biochem.*, **123**:1000-1009 (1998) are pretty well conserved in the protein of the invention, especially the region I containing the DVD motif (positions 163-165) thought to be involved either in UDP binding or in the catalytic process itself.

In addition, the protein of invention has the typical structure of a type II protein. Indeed, it contains a short 28-amino-acid-long N-terminal tail, a transmembrane segment from positions 29 to 49 and a large 278-amino-acid-long C-terminal tail as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10** :685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 94 may play a role in the biosynthesis of polysaccharides, and of the carbohydrate moieties of glycoproteins and glycolipids and/or in cell-cell recognition. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, atherosclerosis, cardiovascular disorders, autoimmune disorders and rheumatic diseases including rheumatoid arthritis.

Protein of SEQ ID NO: 104 (internal designation 108-006-5-0-G2-FL)

The protein of SEQ ID NO: 104 encoded by the extended cDNA SEQ ID NO: 59 shows homology to a neuronal murine protein NP15.6 whose expression is developmentally regulated. NP15.6 protein is encoded by the nucleic acid sequence of Genbank accession number Y08702.

Taken together, these data suggest that the protein of SEQ ID NO: 104 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative disorders and embryogenetic disorders.

C) Proteins homologous to a domain of a protein with known function

Protein of SEQ ID NO: 113 (internal designation 108-009-5-0-A2-FL)

The protein of SEQ ID NO: 113 encoded by the extended cDNA SEQ ID NO: 68 shows extensive homology to the bZIP family of transcription factors, and especially to the human luman protein. (Lu *et al., Mol. Cell. Biol.*, **17** :5117-5126 (1997)). The human luman protein is encoded by the nucleic acid sequence of Genbank accession number : AF009368. The match include the whole bZIP domain composed of a basic DNA-binding domain and of a leucine zipper allowing protein dimerization. The basic domain is conserved in the protein of the invention as shown by the characteristic PROSITE signature (positions 224-237) except for a conservative substitution of a glutamic acid with an aspartic acid in position 233. The typical PROSITE signature for leucine zipper is also present (positions 259 to 280). Secreted proteins may have nucleic acid binding domain as shown by a nematode protein thought to regulate gene expression which exhibits zinc fingers as well as a functional signal peptide (Holst and Zipfel, *J. Biol. Chem.*, 271 :16275-16733, 1996).

Taken together, these data suggest that the protein of SEQ ID NO: 113 may bind to DNA, hence regulating gene expression as a transcription factor. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer.

Proteins of SEQ ID NO: 129 (internal designation 76-13-3-A9-CL1_1)

The protein of SEQ ID NO: 129 encoded by the extended cDNA SEQ ID NO: 84 shows homology with part of a human seven transmembrane protein. The human seven transmembrane protein is encoded by the nucleic acid sequence of Genbank accession number Y11395. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer *et al, Biochem. Biophys. Acta.*, **1395** :301-308 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 129 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Proteins of SEQ ID NO: 95 (internal designation 108-004-5-0-E8-FL)

The protein of SEQ ID NO: 95 encoded by the extended cDNA SEQ ID NO: 50 exhibit the typical PROSITE signature for amino acid permeases (positions 5 to 66) which are integral membrane proteins involved in the transport of amino acids into the cell. In addition, the protein of invention has a transmembrane segment from positions 9 to 29 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10** :685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 95 may be involved in amino acid transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, aminoacidurias, neurodegenerative diseases, anorexia, chronic fatigue, coronary vascular disease, diphtheria, hypoglycemia, male infertility, muscular and myopathies.

As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as,

for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

Oligonucleotide

Complement

Von Heijne matrix

Score

Promoter

Sequence

Transcription start site

Matinspector prediction

Name

TABLE I

SEQ ID NO. in Present Application	Provisional Application Disclosing Sequence	SEQ ID NO. in Provisional Application
40	U.S. Application No. 60/096,116, filed on August 10, 1998	40
41	U.S. Application No. 60/096,116, filed on August 10, 1998	41
42	U.S. Application No. 60/099,273, filed on September 4, 1998	62
43	U.S. Application No. 60/099,273, filed on September 4, 1998	47
44	U.S. Application No. 60/099,273, filed on September 4, 1998	43
45	U.S. Application No. 60/096,116, filed on August 10, 1998	42
46	U.S. Application No. 60/096,116, filed on August 10, 1998	43
47	U.S. Application No. 60/099,273, filed on September 4, 1998	45
48	U.S. Application No. 60/099,273, filed on September 4, 1998	44
49	U.S. Application No. 60/099,273, filed on September 4, 1998	50
50	U.S. Application No. 60/099,273, filed on September 4, 1998	49
51	U.S. Application No. 60/096,116, filed on August 10, 1998	44
52	U.S. Application No. 60/096,116, filed on August 10, 1998	45
53	U.S. Application No. 60/096,116, filed on August 10, 1998	46
54	U.S. Application No. 60/099,273, filed on September 4, 1998	51
55	U.S. Application No. 60/099,273, filed on September 4, 1998	59
56	U.S. Application No. 60/099,273, filed on September 4, 1998	61
57	U.S. Application No. 60/099,273, filed on September 4, 1998	53
58	U.S. Application No. 60/099,273, filed on September 4, 1998	52
59	U.S. Application No. 60/099,273, filed on September 4, 1998	54
60	U.S. Application No. 60/096,116, filed on August 10, 1998	47
61	U.S. Application No. 60/099,273, filed on September 4, 1998	63
62	U.S. Application No. 60/099,273, filed on September 4, 1998	46
63	U.S. Application No. 60/096,116, filed on August 10, 1998	48
64	U.S. Application No. 60/099,273, filed on September 4, 1998	58
65	U.S. Application No. 60/099,273, filed on September 4, 1998	56
66	U.S. Application No. 60/096,116, filed on August 10, 1998	49
67	U.S. Application No. 60/099,273, filed on September 4, 1998	57
68	U.S. Application No. 60/099,273, filed on September 4, 1998	55
69	U.S. Application No. 60/099,273, filed on September 4, 1998	42
70	U.S. Application No. 60/099,273, filed on September 4, 1998	41
71	U.S. Application No. 60/099,273, filed on September 4, 1998	48
72	U.S. Application No. 60/099,273, filed on September 4, 1998	60
73	U.S. Application No. 60/096,116, filed on August 10, 1998	50
74	U.S. Application No. 60/099,273, filed on September 4, 1998	40
75	U.S. Application No. 60/074,121, filed on February 9, 1998	42

SEQ ID NO. in Present Application	Provisional Application Disclosing Sequence	SEQ ID NO. in Provisional Application
76	U.S. Application No. 60/074,121, filed on February 9, 1998	56
77	U.S. Application No. 60/074,121, filed on February 9, 1998	57
78	U.S. Application No. 60/081,563, filed on April 13, 1998	84
79	U.S. Application No. 60/081,563, filed on April 13, 1998	69
80	U.S. Application No. 60/074,121, filed on February 9, 1998	62
81	U.S. Application No. 60/081,563, filed on April 13, 1998	79
82	U.S. Application No. 60/074,121, filed on February 9, 1998	64
83	U.S. Application No. 60/081,563, filed on April 13, 1998	51
84	U.S. Application No. 60/074,121, filed on February 9, 1998	71
130	U.S. Application No. 60/081,563, filed on April 13, 1998	40
131	U.S. Application No. 60/081,563, filed on April 13, 1998	41
132	U.S. Application No. 60/081,563, filed on April 13, 1998	42
133	U.S. Application No. 60/081,563, filed on April 13, 1998	43
134	U.S. Application No. 60/081,563, filed on April 13, 1998	44
135	U.S. Application No. 60/081,563, filed on April 13, 1998	45
136	U.S. Application No. 60/081,563, filed on April 13, 1998	46
137	U.S. Application No. 60/081,563, filed on April 13, 1998	47
138	U.S. Application No. 60/081,563, filed on April 13, 1998	48
139	U.S. Application No. 60/081,563, filed on April 13, 1998	49
140	U.S. Application No. 60/081,563, filed on April 13, 1998	50
141	U.S. Application No. 60/081,563, filed on April 13, 1998	53
142	U.S. Application No. 60/081,563, filed on April 13, 1998	54
143	U.S. Application No. 60/081,563, filed on April 13, 1998	55
144	U.S. Application No. 60/081,563, filed on April 13, 1998	56
145	U.S. Application No. 60/081,563, filed on April 13, 1998	57
146	U.S. Application No. 60/081,563, filed on April 13, 1998	58
147	U.S. Application No. 60/081,563, filed on April 13, 1998	59
148	U.S. Application No. 60/081,563, filed on April 13, 1998	60
149	U.S. Application No. 60/081,563, filed on April 13, 1998	61
150	U.S. Application No. 60/081,563, filed on April 13, 1998	62
151	U.S. Application No. 60/081,563, filed on April 13, 1998	63
152	U.S. Application No. 60/081,563, filed on April 13, 1998	64
153	U.S. Application No. 60/081,563, filed on April 13, 1998	65
154	U.S. Application No. 60/081,563, filed on April 13, 1998	66

TABLE II : Parameters used for each step of EST analysis

	Search Characteristics			Selection Characteristics	
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S=61 X=16	90	17
tRNA	Fasta	both	-	80	60
rRNA	Blastn	both	S=108	80	40
mtRNA	Blastn	both	S=108	80	40
Procaryotic	Blastn	both	S=144	90	40
Fungal	Blastn	both	S=144	90	40
Alu	fasta*	both	-	70	40
L1	Blastn	both	S=72	70	40
Repeats	Blastn	both	S=72	70	40
Promoters	Blastn	top	S=54 X=16	90	15⊥
Vertebrate	fasta*	both	S=108	90	30
ESTs	Blatsn	both	S=108 X=16	90	30
Proteins	blastxη	top	E=0.001	-	-

* use "Quick Fast" Database Scanner

⊥ alignment further constrained to begin closer than 10bp to EST\5' end

η using BLOSUM62 substitution matrix

TABLE III: Parameters used for each step of extended cDNA analysis

	Search characteristics		Selection characteristics			
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments
miscellaneous*	FASTA	both	-	90	15	
tRNA$	FASTA	both	-	80	90	
rRNA$	BLASTN	both	S=108	80	40	
mtRNA$	BLASTN	both	S=108	80	40	
Procaryotic$	BLASTN	both	S=144	90	40	
Fungal*	BLASTN	both	S=144	90	40	
Alu*	BLASTN	both	S=72	70	40	max 5 matches, masking
L1$	BLASTN	both	S=72	70	40	max 5 matches, masking
Repeats$	BLASTN	both	S=72	70	40	masking
PolyA	BLAST2N	top	W=6,S=10,E=1000	90	8	in the last 20 nucleotides
Polyadenylation signal	-	top	AATAAA allowing 1 mismatch			in the 50 nucleotides preceding the 5' end of the polA
Vertibrate*	BLASTN then FASTA	both	-	90 then 70	30	first BLASTN and then FASTA on matching sequences
ESTs*	BLAST2N	both	-	90	30	
Geneseq	BLASTN	both	W=8, B=10	90	30	
ORF	BLASTP	top	W=8, B=10	-	-	on ORF proteins, max 10 matches
Proteins*	BLASTX	top	E=0.001	70	30	

$ steps common to EST analysis and using the same algorithms and parameters

* steps also used in EST analysis but with different algorithms and/or parameters

TABLE IV

Id	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
40	35 through 568	35 through 100	101 through 568	569	667 through 672	685 through 699
41	68 through 337	68 through 124	125 through 337	338	462 through 467	482 through 497
42	39 through 413	39 through 83	84 through 413	414	566 through 571	583 through 598
43	235 through 642	235 through 336	337 through 642	643	1540 through 1545	1564 through 1579
44	42 through 755	42 through 200	201 through 755	756	860 through 865	878 through 893
45	23 through 340	23 through 235	236 through 340	341	611 through 616	629 through 644
46	12 through 380	12 through 263	264 through 380	381	-	523 through 538
47	8 through 232	8 through 154	155 through 232	233	-	737 through 752
48	183 through 422	183 through 302	303 through 422	423	505 through 510	523 through 537
49	24 through 1004	24 through 170	171 through 1004	1005	-	1586 through 1602
50	80 through 784	80 through 139	140 through 784	785	910 through 915	933 through 948
51	67 through 222	67 through 159	160 through 222	223	-	673 through 687
52	46 through 732	46 through 186	187 through 732	733	781 through 786	806 through 821
53	81 through 356	81 through 152	153 through 356	357	406 through 411	429 through 445
54	72 through 1346	72 through 140	141 through 1346	1347	1482 through 1487	1502 through 1517
55	194 through 454	194 through 379	380 through 454	455	-	1545 through 1560
56	48 through 494	48 through 347	348 through 494	495	1031 through 1036	1051 through 1066
57	111 through 671	111 through 215	216 through 671	672	990 through 995	1045 through 1061
58	5 through 373	5 through 82	83 through 373	374	1986 through 1991	2010 through 2025
59	14 through 472	14 through 319	320 through 472	473	555 through 560	576 through 591
60	2 through 217	-	2 through 217	218	489 through 494	529 through 544
61	51 through 575	51 through 110	111 through 575	576	1653 through 1658	1674 through 1689
62	69 through 977	69 through 128	129 through 977	978	1076 through 1081	1096 through 1111
63	44 through 238	44 through 160	161 through 238	239	443 through 448	540 through 554
64	114 through 524	114 through 164	165 through 524	525	1739 through 1744	1758 through 1773
65	26 through 487	26 through 64	65 through 487	488	883 through 888	901 through 917
66	80 through 388	80 through 187	188 through 388	389	609 through 614	627 through 641

Id	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
67	186 through 443	186 through 407	408 through 443	444	827 through 832	839 through 854
68	75 through 1259	75 through 1004	1005 through 1259	1260	1536 through 1541	1553 through 1568
69	98 through 376	98 through 151	152 through 376	377	471 through 476	491 through 506
70	72 through 254	72 through 134	135 through 254	255	506 through 511	528 through 542
71	148 through 1140	148 through 240	241 through 1140	1141	1590 through 1595	1614 through 1629
72	109 through 738	109 through 405	406 through 738	739	1633 through 1638	1650 through 1665
73	55 through 291	55 through 255	256 through 291	292	390 through 395	410 through 425
74	25 through 276	-	25 through 276	277	508 through 513	533 through 546
75	32 through 307	32 through 91	92 through 307	308	452 through 457	472 through 485
76	46 through 675	46 through 87	88 through 675	676	1363 through 1368	1382 through 1394
77	329 through 943	329 through 745	746 through 943	944	-	1322 through 1333
78	27 through 281	27 through 77	78 through 281	282	-	-
79	61 through 405	61 through 213	214 through 405	406	675 through 680	692 through 703
80	137 through 379	137 through 229	230 through 379	380	728 through 733	755 through 768
81	37 through 741	37 through 153	154 through 741	742	969 through 974	994 through 1007
82	80 through 265	80 through 142	143 through 265	266	491 through 496	517 through 527
83	612 through 644	-	612 through 644	645	829 through 834	850 through 861
84	61 through 228	61 through 162	163 through 228	229	208 through 213	-
130	15 through 311	15 through 110	111 through 311	312	507 through 512	531 through 542
131	50 through 529	50 through 130	131 through 529	530	877 through 882	899 through 909
132	240 through 416	240 through 305	306 through 416	417	1117 through 1122	1139 through 1149
133	111 through 446	111 through 254	255 through 446	447	890 through 895	909 through 921
134	123 through 455	123 through 290	291 through 455	456	886 through 891	904 through 916
135	2 through 433	2 through 232	233 through 433	434	488 through 493	510 through 520
136	34 through 363	34 through 87	88 through 363	364	536 through 541	558 through 568
137	50 through 286	50 through 157	158 through 286	287	385 through 390	405 through 416
138	50 through 637	50 through 151	152 through 637	638	-	1277 through 1289
139	72 through 602	72 through 125	126 through 602	603	-	704 through 715
140	120 through	120 through 185	186 through 434	435	899 through 904	918 through 931

Id	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
	434					
141	4 through 447	4 through 147	148 through 447	448	858 through 863	880 through 891
142	28 through 804	28 through 96	97 through 804	805	-	806 through 817
143	27 through 359	27 through 212	213 through 359	360	988 through 993	1009 through 1020
144	25 through 957	25 through 93	94 through 957	958	1368 through 1373	1388 through 1399
145	47 through 319	47 through 226	227 through 319	320	-	656 through 666
146	80 through 940	80 through 130	131 through 940	941	1101 through 1106	1119 through 1130
147	146 through 457	146 through 292	293 through 457	458	442 through 447	465 through 475
148	100 through 351	100 through 207	208 through 351	352	-	940 through 949
149	177 through 569	177 through 236	237 through 569	570	-	931 through 939
150	67 through 459	67 through 135	136 through 459	460	856 through 861	875 through 887
151	65 through 1069	65 through 112	113 through 1069	1070	1978 through 1983	1999 through 2010
152	70 through 321	70 through 234	235 through 321	322	364 through 369	375 through 387
153	38 through 877	38 through 91	92 through 877	878	947 through 952	974 through 983
154	51 through 470	51 through 203	204 through 470	471	1585 through 1590	1604 through 1614

TABLE V

Id	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
85	-22 through 156	-22 through -1	1 through 156
86	-19 through 71	-19 through -1	1 through 71
87	-15 through 110	-15 through -1	1 through 110
88	-34 through 102	-34 through -1	1 through 102
89	-53 through 185	-53 through -1	1 through 185
90	-71 through 35	-71 through -1	1 through 35
91	-84 through 39	-84 through -1	1 through 39
92	-49 through 26	-49 through -1	1 through 26
93	-40 through 40	-40 through -1	1 through 40
94	-49 through 278	-49 through -1	1 through 278
95	-20 through 215	-20 through -1	1 through 215
96	-31 through 21	-31 through -1	1 through 21
97	-47 through 182	-47 through -1	1 through 182
98	-24 through 68	-24 through -1	1 through 68
99	-23 through 402	-23 through -1	1 through 402
100	-62 through 25	-62 through -1	1 through 25
101	-100 through 49	-100 through -1	1 through 49
102	-35 through 152	-35 through -1	1 through 152
103	-26 through 97	-26 through -1	1 through 97
104	-102 through 51	-102 through -1	1 through 51
105	1 through 72	-	1 through 72
106	-20 through 155	-20 through -1	1 through 155
107	-20 through 283	-20 through -1	1 through 283
108	-39 through 26	-39 through -1	1 through 26
109	-17 through 120	-17 through -1	1 through 120
110	-13 through 141	-13 through -1	1 through 141
111	-36 through 67	-36 through -1	1 through 67
112	-74 through 12	-74 through -1	1 through 12
113	-310 through 85	-310 through -1	1 through 85
114	-18 through 75	-18 through -1	1 through 75
115	-21 through 40	-21 through -1	1 through 40
116	-31 through 300	-31 through -1	1 through 300
117	-99 through 111	-99 through -1	1 through 111
118	-67 through 12	-67 through -1	1 through 12
119	1 through 84	-	1 through 84
120	-20 through 72	-20 through -1	1 through 72
121	-14 through 196	-14 through -1	1 through 196

Id	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
122	-139 through 66	-139 through -1	1 through 66
123	-17 through 68	-17 through -1	1 through 68
124	-51 through 64	-51 through -1	1 through 64
125	-31 through 50	-31 through -1	1 through 50
126	-39 through 196	-39 through -1	1 through 196
127	-21 through 41	-21 through -1	1 through 41
128	1 through 11	-	1 through 11
129	-34 through 22	-34 through -1	1 through 22
155	-32 through 67	-32 through -1	1 through 67
156	-27 through 133	-27 through -1	1 through 133
157	-22 through 37	-22 through -1	1 through 37
158	-48 through 64	-48 through -1	1 through 64
159	-56 through 55	-56 through -1	1 through 55
160	-77 through 67	-77 through -1	1 through 67
161	-18 through 92	-18 through -1	1 through 92
162	-36 through 43	-36 through -1	1 through 43
163	-34 through 162	-34 through -1	1 through 162
164	-18 through 159	-18 through -1	1 through 159
165	-22 through 83	-22 through -1	1 through 83
166	-48 through 100	-48 through -1	1 through 100
167	-23 through 236	-23 through -1	1 through 236
168	-62 through 49	-62 through -1	1 through 49
169	-23 through 288	-23 through -1	1 through 288
170	-60 through 31	-60 through -1	1 through 31
171	-17 through 270	-17 through -1	1 through 270
172	-49 through 55	-49 through -1	1 through 55
173	-36 through 48	-36 through -1	1 through 48
174	-20 through 111	-20 through -1	1 through 111
175	-23 through 108	-23 through -1	1 through 108
176	-16 through 319	-16 through -1	1 through 319
177	-55 through 29	-55 through -1	1 through 29
178	-18 through 262	-18 through -1	1 through 262
179	-51 through 89	-51 through -1	1 through 89

TABLE VI

Id	Collection refs	Deposit Name
40	ATCC# 98921	SignalTag 121-144
41	ATCC# 98921	SignalTag 121-144
42	ATCC# 98919	SignalTag 145-165
43	ATCC# 98919	SignalTag 145-165
44	ATCC# 98919	SignalTag 145-165
45	ATCC# 98921	SignalTag 121-144
46	ATCC# 98921	SignalTag 121-144
47	ATCC# 98919	SignalTag 145-165
48	ATCC# 98919	SignalTag 145-165
49	ATCC# 98919	SignalTag 145-165
50	ATCC# 98919	SignalTag 145-165
51	ATCC# 98921	SignalTag 121-144
52	ATCC# 98921	SignalTag 121-144
53	ATCC# 98921	SignalTag 121-144
54	ATCC# 98919	SignalTag 145-165
55	ATCC# 98919	SignalTag 145-165
56	ATCC# 98919	SignalTag 145-165
57	ATCC# 98919	SignalTag 145-165
58	ATCC# 98919	SignalTag 145-165
59	ATCC# 98919	SignalTag 145-165
60	ATCC# 98921	SignalTag 121-144
61	ATCC# 98919	SignalTag 145-165
62	ATCC# 98919	SignalTag 145-165
63	ATCC# 98921	SignalTag 121-144
64	ATCC# 98919	SignalTag 145-165
65	ATCC# 98919	SignalTag 145-165
66	ATCC# 98921	SignalTag 121-144
67	ATCC# 98919	SignalTag 145-165
68	ATCC# 98919	SignalTag 145-165
69	ATCC# 98919	SignalTag 145-165
70	ATCC# 98919	SignalTag 145-165
71	ECACC# XXXX	Signal Tag 28011 999
72	ECACC# XXXX	Signal Tag 28011 999
73	ECACC# XXXX	Signal Tag 28011 999
74	ECACC# XXXX	Signal Tag 28011 999
75	ECACC# XXXX	Signal Tag 28011 999
76	ECACC# XXXX	Signal Tag 28011 999
77	ECACC# XXXX	Signal Tag 28011 999
78	ECACC# XXXX	Signal Tag 28011 999
79	ECACC# XXXX	Signal Tag 28011 999
80	ECACC# XXXX	Signal Tag 28011 999
81	ECACC# XXXX	Signal Tag 28011 999
82	ECACC# XXXX	Signal Tag 28011 999
83	ECACC# XXXX	Signal Tag 28011 999
84	ECACC# XXXX	Signal Tag 28011 999

TABLE VII

Internal designation	Id	Type of sequence
108-002-5-0-B1-FL	40	DNA
108-002-5-0-F3-FL	41	DNA
108-002-5-0-F4-FL	42	DNA
108-003-5-0-A8-FL	43	DNA
108-003-5-0-D2-FL	44	DNA
108-003-5-0-E5-FL	45	DNA
108-003-5-0-H2-FL	46	DNA
108-004-5-0-B7-FL	47	DNA
108-004-5-0-C8-FL	48	DNA
108-004-5-0-D10-FL	49	DNA
108-004-5-0-E8-FL	50	DNA
108-004-5-0-F5-FL	51	DNA
108-004-5-0-G6-FL	52	DNA
108-005-5-0-B11-FL	53	DNA
108-005-5-0-C1-FL	54	DNA
108-005-5-0-F11-FL	55	DNA
108-005-5-0-F6-FL	56	DNA
108-006-5-0-C2-FL	57	DNA
108-006-5-0-E6-FL	58	DNA
108-006-5-0-G2-FL	59	DNA
108-006-5-0-G4-FL	60	DNA
108-008-5-0-A6-FL	61	DNA
108-008-5-0-A8-FL	62	DNA
108-008-5-0-C10-FL	63	DNA
108-008-5-0-E6-FL	64	DNA
108-008-5-0-F6-FL	65	DNA
108-008-5-0-G12-FL	66	DNA
108-008-5-0-G4-FL	67	DNA
108-009-5-0-A2-FL	68	DNA
108-013-5-0-C12-FL	69	DNA
108-013-5-0-G11-FL	70	DNA
108-003-5-0-E4-FL	71	DNA
108-005-5-0-D6-FL	72	DNA
108-008-5-0-G3-FL	73	DNA
108-013-5-0-B5-FL	74	DNA
26-44-1-B5-CL3_1	75	DNA
47-4-4-C6-CL2_3	76	DNA
47-40-4-G9-CL1_1	77	DNA
48-25-4-D8-CL1_7	78	DNA
48-28-3-A9-CL0_1	79	DNA
51-25-1-A2-CL3_1	80	DNA
55-10-3-F5-CL0_3	81	DNA
57-19-2-G8-CL1_3	82	DNA
58-34-2-H8-CL1_3	83	DNA
76-13-3-A9-CL1_1	84	DNA
78-7-2-B8-FL1	130	DNA
77-8-4-F9-FL1	131	DNA
58-8-1-F2-FL2	132	DNA

Internal designation	Id	Type of sequence
77-13-1-A7-FL2	133	DNA
47-2-3-G9-FL1	134	DNA
33-75-4-H7-FL1	135	DNA
51-41-1-F10-FL1	136	DNA
48-51-4-C11-FL1	137	DNA
33-58-3-C8-FL1	138	DNA
76-20-4-C11-FL1	139	DNA
76-28-3-A12-FL1	140	DNA
76-25-4-F11-FL1	141	DNA
58-20-4-G7-FL1	142	DNA
33-54-1-B9-FL1	143	DNA
76-20-3-H1-FL1	144	DNA
47-20-2-G3-FL1	145	DNA
78-25-1-H11-FL1	146	DNA
78-6-2-B10-FL1	147	DNA
58-49-3-G10-FL1	148	DNA
78-21-1-B7-FL1	149	DNA
57-28-4-B12-FL1	150	DNA
33-77-4-E2-FL1	151	DNA
58-19-3-D3-FL2	152	DNA
37-7-4-E7-FL1	153	DNA
60-14-2-H10-FL1	154	DNA
108-002-5-0-B1-FL	85	PRT
108-002-5-0-F3-FL	86	PRT
108-002-5-0-F4-FL	87	PRT
108-003-5-0-A8-FL	88	PRT
108-003-5-0-D2-FL	89	PRT
108-003-5-0-E5-FL	90	PRT
108-003-5-0-H2-FL	91	PRT
108-004-5-0-B7-FL	92	PRT
108-004-5-0-C8-FL	93	PRT
108-004-5-0-D10-FL	94	PRT
108-004-5-0-E8-FL	95	PRT
108-004-5-0-F5-FL	96	PRT
108-004-5-0-G6-FL	97	PRT
108-005-5-0-B11-FL	98	PRT
108-005-5-0-C1-FL	99	PRT
108-005-5-0-F11-FL	100	PRT
108-005-5-0-F6-FL	101	PRT
108-006-5-0-C2-FL	102	PRT
108-006-5-0-E6-FL	103	PRT
108-006-5-0-G2-FL	104	PRT
108-006-5-0-G4-FL	105	PRT
108-008-5-0-A6-FL	106	PRT
108-008-5-0-A8-FL	107	PRT
108-008-5-0-C10-FL	108	PRT
108-008-5-0-E6-FL	109	PRT
108-008-5-0-F6-FL	110	PRT
108-008-5-0-G12-FL	111	PRT
108-008-5-0-G4-FL	112	PRT
108-009-5-0-A2-FL	113	PRT

Internal designation	Id	Type of sequence
108-013-5-0-C12-FL	114	PRT
108-013-5-0-G11-FL	115	PRT
108-003-5-0-E4-FL	116	PRT
108-005-5-0-D6-FL	117	PRT
108-008-5-0-G3-FL	118	PRT
108-013-5-0-B5-FL	119	PRT
26-44-1-B5-CL3_1	120	PRT
47-4-4-C6-CL2_3	121	PRT
47-40-4-G9-CL1_1	122	PRT
48-25-4-D8-CL1_7	123	PRT
48-28-3-A9-CL0_1	124	PRT
51-25-1-A2-CL3_1	125	PRT
55-10-3-F5-CL0_3	126	PRT
57-19-2-G8-CL1_3	127	PRT
58-34-2-H8-CL1_3	128	PRT
76-13-3-A9-CL1_1	129	PRT
78-7-2-B8-FL1	155	PRT
77-8-4-F9-FL1	156	PRT
58-8-1-F2-FL2	157	PRT
77-13-1-A7-FL2	158	PRT
47-2-3-G9-FL1	159	PRT
33-75-4-H7-FL1	160	PRT
51-41-1-F10-FL1	161	PRT
48-51-4-C11-FL1	162	PRT
33-58-3-C8-FL1	163	PRT
76-20-4-C11-FL1	164	PRT
76-28-3-A12-FL1	165	PRT
76-25-4-F11-FL1	166	PRT
58-20-4-G7-FL1	167	PRT
33-54-1-B9-FL1	168	PRT
76-20-3-H1-FL1	169	PRT
47-20-2-G3-FL1	170	PRT
78-25-1-H11-FL1	171	PRT
78-6-2-B10-FL1	172	PRT
58-49-3-G10-FL1	173	PRT
78-21-1-B7-FL1	174	PRT
57-28-4-B12-FL1	175	PRT
33-77-4-E2-FL1	176	PRT
58-19-3-D3-FL2	177	PRT
37-7-4-E7-FL1	178	PRT
60-14-2-H10-FL1	179	PRT

TABLE VIII

Id	Locations	PROSITE signature Name
89	205-226	Leucine zipper
95	5-66	Amino acid permease
103	46-67	Leucine zipper
113	259-280	Leucine zipper
120	27-40	MAT8 family
122	123-125	Cell attachment sequence

CLAIMS

1. A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-84 and 130-154 or a sequence complementary thereto.

2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-84 and 130-154 or one of the sequences complementary thereto.

3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-59, 61-73, 75, 77-82, and 130-154 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.

4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-59, 61-75, 77-82, and 130-154 which encode a mature protein.

5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-59, 61-73, 75-82, 84, and 130-154 which encode the signal peptide.

6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 85-129 and 155-179.

7. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 85-104, 106-120, 122-127, and 155-179.

8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 85-104, 106-118, 120-127, 129, and 155-179.

9. A purified or isolated protein comprising the sequence of one of SEQ ID NOs: 85-129 and 155-179.

10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 85-129 and 155-179.

11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 85-104, 106-118, 120-127, 129, and 155-179.

12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 85-104, 106-120, 122-127, and 155-179.

13. A method of making a protein comprising one of the sequences of SEQ ID NO: 85-129 and 155-179, comprising the steps of:

obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-84 and 130-154;

inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and

introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said cDNA.

14. The method of Claim 13, further comprising the step of isolating said protein.

15. A protein obtainable by the method of Claim 14.

16. A host cell containing a recombinant nucleic acid of Claim 1.

17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 85-129 and 155-179.

18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-84 and 130-154, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-84 and 130-154, or a fragment thereof of at least 15 consecutive nucleotides.

19 A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-84 and 130-154 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-84 and 130-154.

20 A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 85-129 and 155-179.

21 A computer readable medium having stored thereon a sequence selected from the group consisting of a cDNA code of SEQ ID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179.

22 A computer system comprising a processor and a data storage device wherein said data storage device has stored thereon a sequence selected from the group consisting of a cDNA code of SEQ ID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179.

23 The computer system of Claim 22 further comprising a sequence comparer and a data storage device having reference sequences stored thereon.

24 The computer system of Claim 23 wherein said sequence comparer comprises a computer program which indicates polymorphisms.

25 The computer system of Claim 22 further comprising an identifier which identifies features in said sequence.

26 A method for comparing a first sequence to a reference sequence wherein said first sequence is selected from the group consisting of a cDNA code of SEQID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179 comprising the steps of:

reading said first sequence and said reference sequence through use of a computer program which compares sequences; and

determining differences between said first sequence and said reference sequence with said computer program.

27 The method of Claim 26, wherein said step of determining differences between the first sequence and the reference sequence comprises identifying polymorphisms.

28 A method for identifying a feature in a sequence selected from the group consisting of a cDNA code of SEQ ID NOs. 40-84 and 130-154 and a polypeptide code of SEQ ID NOs. 85-129 and 155-179 comprising the steps of:

reading said sequence through the use of a computer program which identifies features in sequences; and

identifying features in said sequence with said computer program.

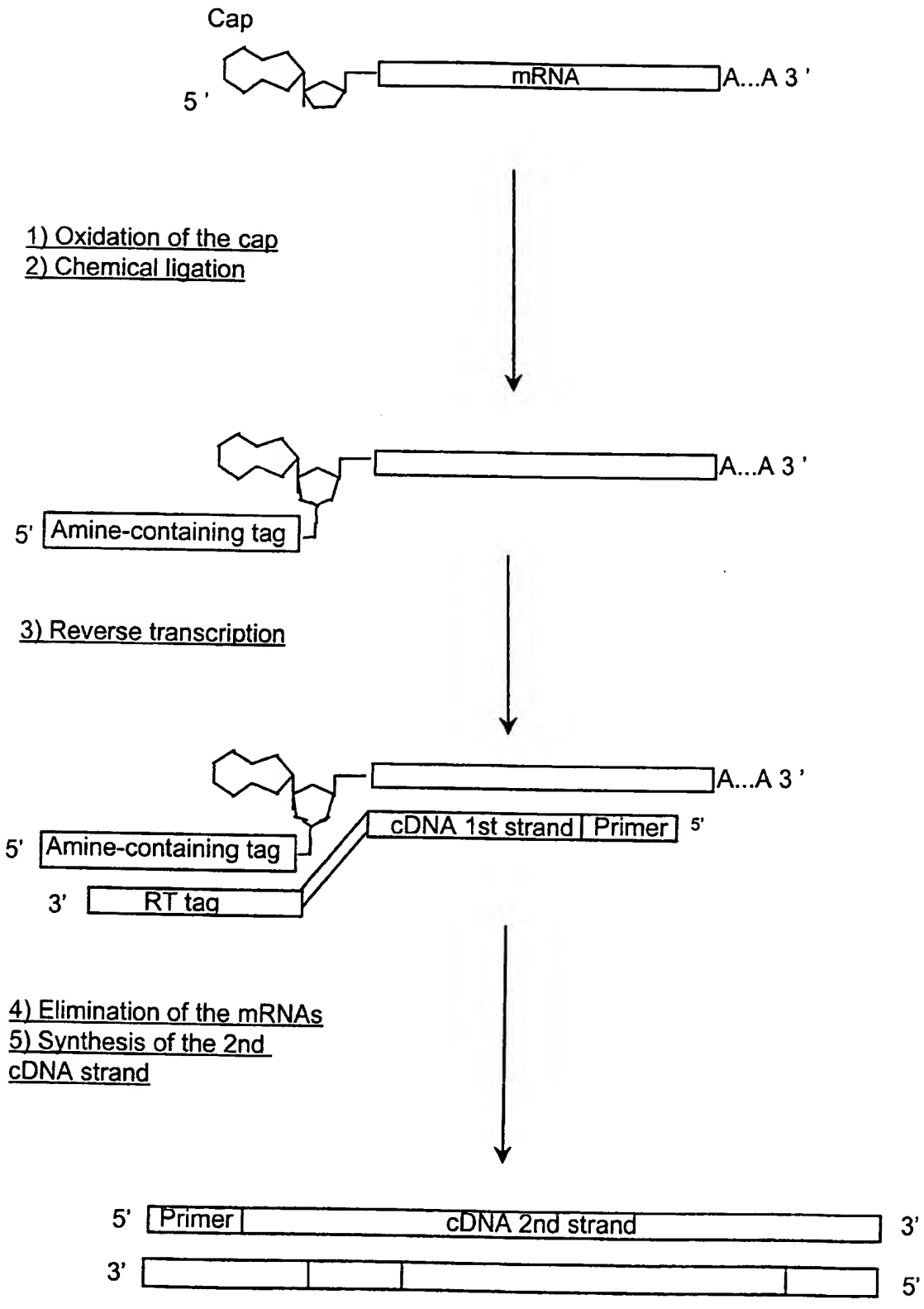

Cap
5'
mRNA
A...A 3'
1) Oxidation of the cap
2) Chemical ligation
A...A 3'
5'
Amine-containing tag
3) Reverse transcription
A...A 3'
cDNA 1st strand
Primer
5'
5'
Amine-containing tag
3'
RT tag
4) Elimination of the mRNAs
5) Synthesis of the 2nd cDNA strand
5'
Primer
cDNA 2nd strand
3'
3'
5'

Figure 1

Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

FIGURE 2

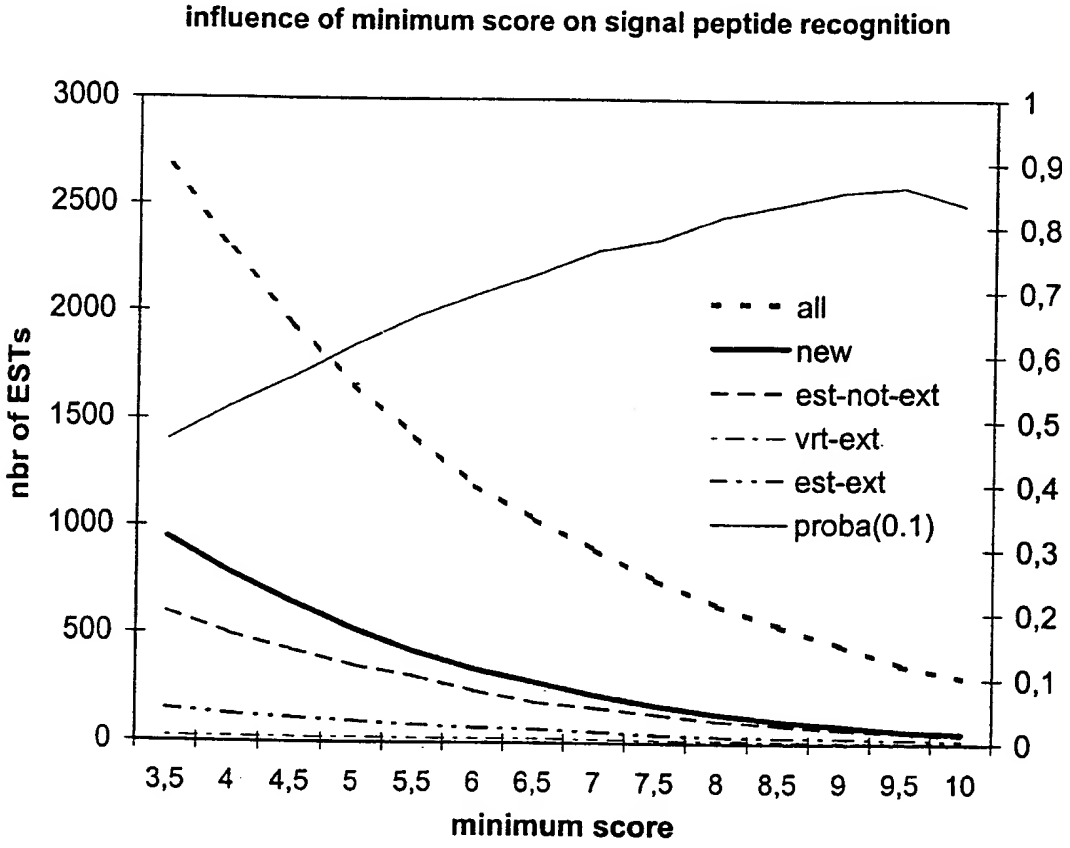

influence of minimum score on signal peptide recognition
nbr of ESTs
3000
2500
2000
1500
1000
500
0
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
3,5
4
4,5
5
5,5
6
6,5
7
7,5
8
8,5
9
9,5
10
minimum score
all
new
est-not-ext
vrt-ext
est-ext
proba(0.1)

FIGURE 3

Minimum signal peptide score	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

FIGURE 4

Tissue	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	9	1	0	6
Colon	21	11	4	0	0
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	0	0
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	0	0
Large intestine	21	8	4	0	1
Liver	23	9	6	0	0
Lung	24	12	4	0	1
Lung (cells)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	0
Prostate	34	16	4	0	2
Spleen	56	28	10	0	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	1	0
Testis	131	68	25	1	8
Thyroid	17	8	2	0	2
Umbilical cord	55	17	12	1	3
Uterus	28	15	3	0	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150

FIGURE 5

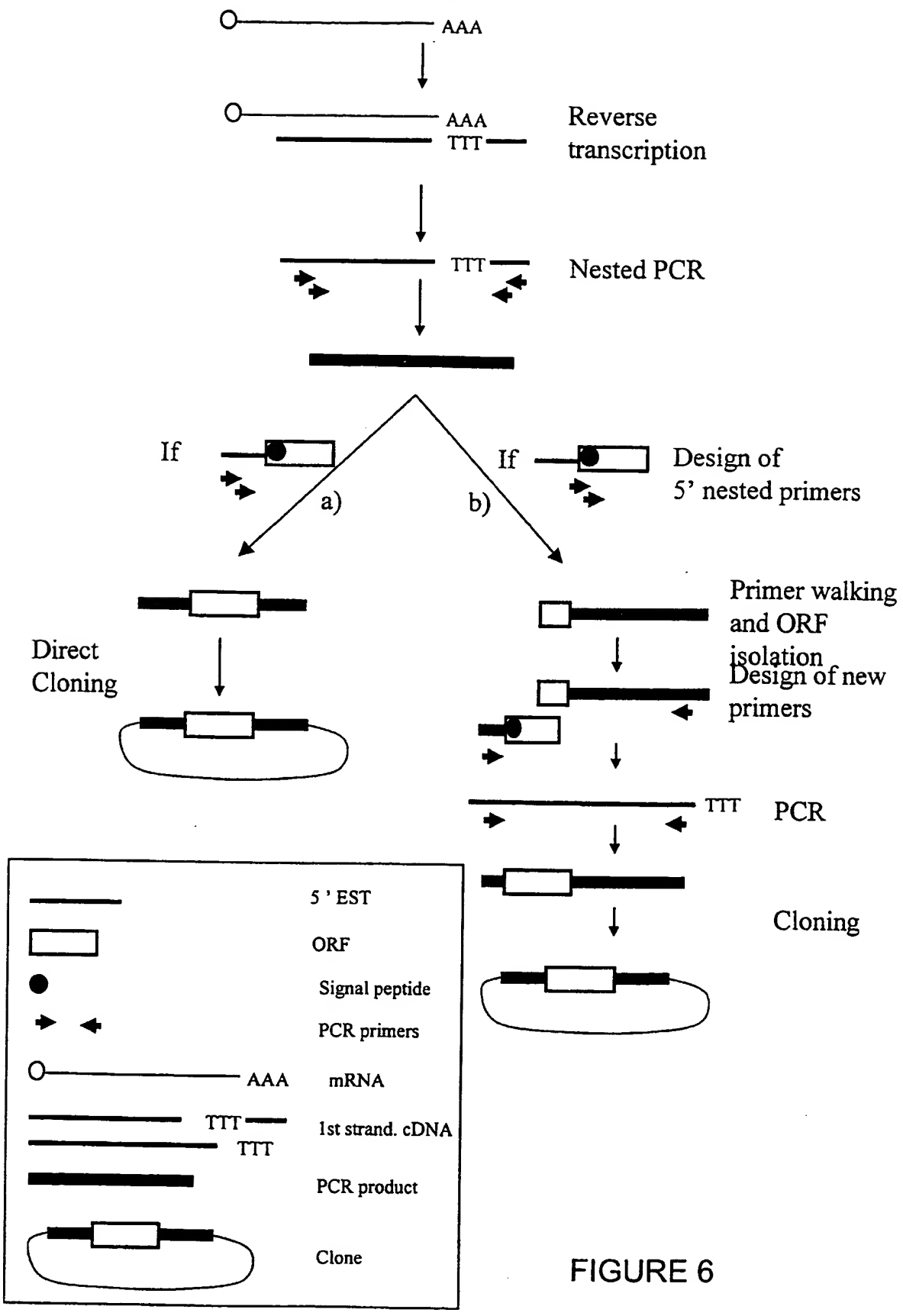
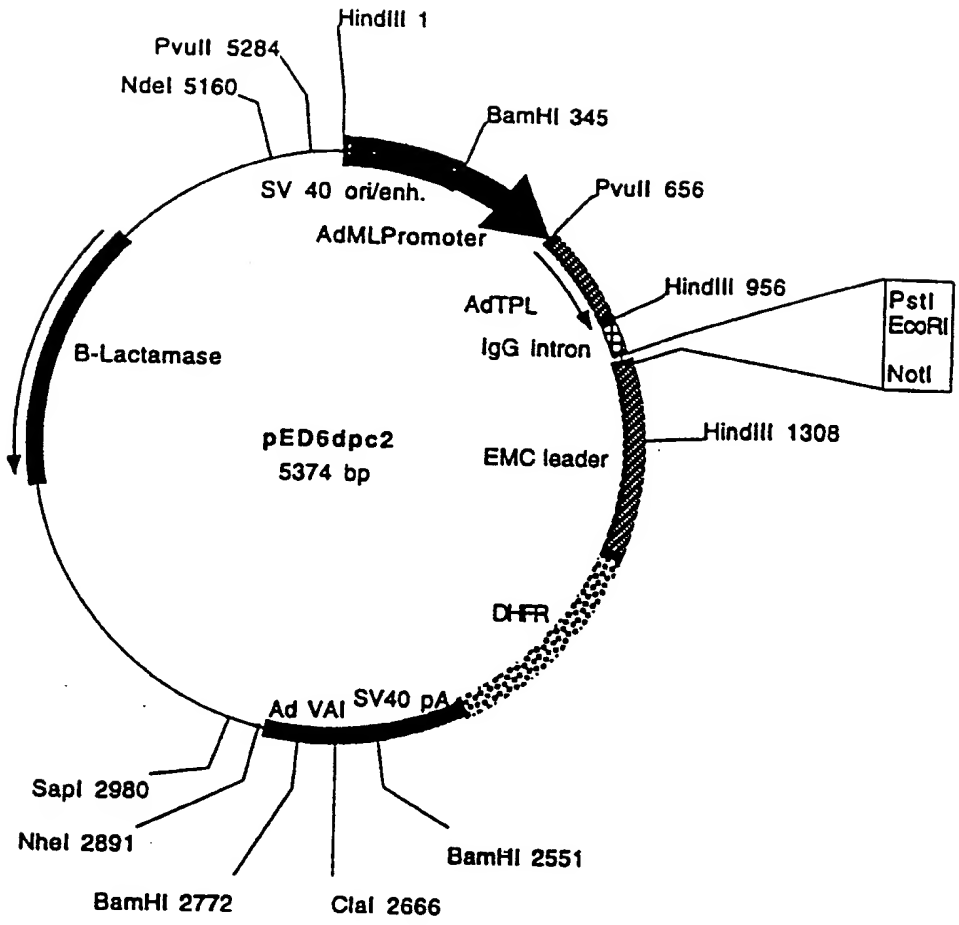

AAA
AAA
TTT
Reverse transcription
TTT
Nested PCR
If
a)
b)
If
Design of 5' nested primers
Direct Cloning
Primer walking and ORF isolation
Design of new primers
TTT
PCR
Cloning
5 ' EST
ORF
Signal peptide
PCR primers
AAA
mRNA
TTT
TTT
1st strand. cDNA
PCR product
Clone

FIGURE 6



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

FIGURE 7

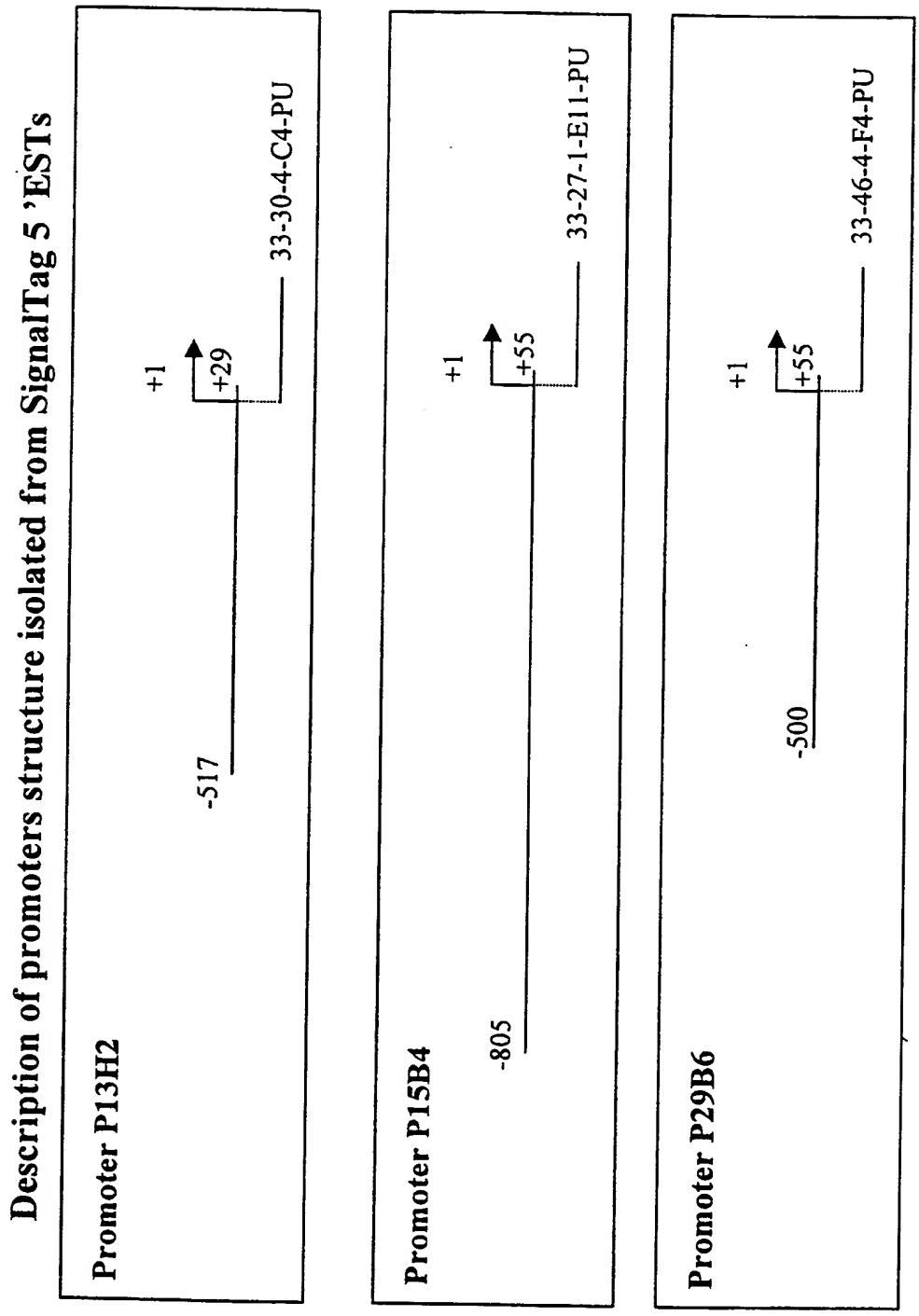

Description of promoters structure isolated from SignalTag 5 'ESTs
Promoter P13H2
+1
+29
-517
33-30-4-C4-PU
Promoter P15B4
+1
+55
-805
33-27-1-E11-PU
Promoter P29B6
+1
+55
-500
33-46-4-F4-PU

FIGURE 8

Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	-	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	-	0.960	11	GCACACCTCAG
GATA_C	-364	-	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	-	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

Promoter sequence P15B4 (861bp) :

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

Promoter sequence P29B6 (555 bp) :

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

97.8% identity in 92 aa overlap

```
                        10         20         30         40         50         60
SEQ ID NO:120 MASLGHILVFCVGLLTMAKAESPKEHDPFTYDYQSLQIGGLVIAGILFILGILIVLSRRC
              ::.: ::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ ID NO:180 MAPLHHILVFCVGLLTMAKAESPKEHDPFTYDYQSLQIGGLVIAGILFILGILIVLSRRC
                        10         20         30         40         50         60

                        70         80         90
SEQ ID NO:120 RCKFNQQQRTGEPDEEEGTFRSSIRRLSTRRR
              ::::::::::::::::::::::::::::::::
SEQ ID NO:180 RCKFNQQQRTGEPDEEEGTFRSSIRRLSTRRR
                        70         80         90
```

FIGURE 10

98.6% identity in 210 aa overlap

```
                                                          10        20        30
SEQ ID NO:121                                             MLTLLGLSLILAGLIVGGACIYKHFMPKST
                                                          :::::::::::::::::::::::::::::
SEQ ID NO:181 LLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILAGLIVGGACIYKYFMPKST
                    30        40        50        60        70        80

                           40        50        60        70        80        90
SEQ ID NO:121 IYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDVPVPSFSDSDPAAIIH
              :::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ ID NO:181 IYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDVPVPSFSDSDPAAIIH
                    90        100       110       120       130       140

                         100       110       120       130       140       150
SEQ ID NO:121 DFEKGMTAYLDLLLGNCYLMPLNTSIVMPPENLVELFGKLASGRYLPQTYVVREDLVAVE
              ::::::::::::::::::::::::::::::::.:::::::::::::::::::::::::::::
SEQ ID NO:181 DFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLASGRYLPQTYVVREDLVAVE
                   150       160       170       180       190       200

                         160       170       180       190       200       210
SEQ ID NO:121 EIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIRHFPNEFIVETKICQE
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ ID NO:181 EIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIRHFPNEFIVETKICQE
                   210       220       230       240       250       260
```

FIGURE 11

83.4% identity in 211 aa overlap

```
                                                    10        20        30
SEQ ID NO:128                                       LWWFWLLWTVLILFSCCCAFRHRRAKLRLQ
                                                    ::::::::::::::::::::::::::::::
SEQ ID NO:182 ELCPGVNTQPYLCETGHCCGETGCCTYYYELWWFWLLWTVLILFSCCCAFRHRRAKLRLQ
                     70        80        90       100       110       120

                     40        50        60        70        80        90
SEQ ID NO:128 QQQRQREINLLAYHGACHGAGPFPTGSLLDLRLLSTFKPPAYEDVVHRPGTPPPPYTVAP
              :::::::::::::::::::: :::::::::::.:::::::::.:::::::::.:
SEQ ID NO:182 QQQRQREINLLAYHGACHGAGPVPTGSLLDLRLLSAFKPPAYEDVVHHPGTPPPPYTVGP
                    130       140       150       160       170       180

                    100       110       120       130       140       150
SEQ ID NO:128 GRPLTASSEQTCCSSSSSCPAHFEGTNVEGVSSHQSAPPHQEGEPGAGVTPASTPPSCRY
              : : :.::: : :::.:::.::.:::::::::::.::: ::::::: ::..:. .:::::::
SEQ ID NO:182 GYPWTTSSECTRCSSESSCSAHLEGTNVEGVSSQQSALPHQEGEPRAGLSPVHIPPSCRY
                    190       200       210       220       230       240

                    160       170       180       190       200       210
SEQ ID NO:128 RRLTGDSGIELCPCPASGEGEPVKEVRVSATLPDLEDYSPCALPPESVPQIFPMGLSSSE
              :::::::::::::::.:.::::.::.:.::. :::::.:::::::::.::.:. :::::.::
SEQ ID NO:182 RRLTGDSGIELCPCPDSSEGEPLKEARASASQPDLEDHSPCALPPDSVSQVPPMGLASSC
                    250       260       270       280       290       300

SEQ ID NO:128 GDIP
              :
SEQ ID NO:182 GTSHK
```

FIGURE 12

SEQUENCE LISTING

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<151> 1998-04-13
<150> 60/096,116
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<160> 182
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<223> In vitro transcription product
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<223> modified_base
<222> (1)...(1)
<223> m7g added to 1
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<211> 46
<212> RNA
<213> Artificial Sequence
<220>
<223> In vitro transcription product
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<400> 2
gcauccuacu cccauccaau uccacccuaa cuccucccau cuccac 46
<210> 3
<211> 25
<212> DNA
<213> Artificial Sequence
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<223> In vitro transcription product
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<211> 25
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<223> Oligonucleotide
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taatggtctc gtgcgaattc ttgat 25
<210> 5
<211> 25
<212> DNA
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ccgacaagac caacgtcaag gccgc 25
<210> 6

<211> 25
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agtgattcct gctactttgg atggc 25
<210> 8
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<212> DNA
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<223> Oligonucleotide
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gcttggtctt gttctggagt ttaga 25
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atgggaaagg aaaagactca tatca 25
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agcagcaaca atcaggacag cacag 25
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atcaagaatt cgcacgagac catta 25
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tttttvn 67
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ccagcagagt cacgagagag actacacgg 29
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cacgagagag actacacggt actgg 25
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gagagaaaga actgactgar acgtttgag atg aag aaa gtt ctc ctc ctg atc 113
Met Lys Lys Val Leu Leu Leu Ile
-15 -10
aca gcc atc ttg gca gtg gct gtw ggt ttc cca gtc tct caa gac cag 161
Thr Ala Ile Leu Ala Val Ala Val Gly Phe Pro Val Ser Gln Asp Gln
-5 1 5
gaa cga gaa aaa aga agt atc agt gac agc gat gaa tta gct tca ggr 209
Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly
10 15 20
wtt ttt gtg ttc cct tac cca tat cca ttt cgc cca ctt cca cca att 257
Xaa Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile
25 30 35

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cca ttt cca aga ttt cca tgg ttt aga cgt aan ttt cct att cca ata      305
Pro Phe Pro Arg Phe Pro Trp Phe Arg Arg Xaa Phe Pro Ile Pro Ile
40                  45                  50                  55
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa      354
Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys
                60                  65
ggaaaagtca cratаaacct ggtcacctga aattgaaatt gagccacttc cttgaaraat    414
caaaattcct gttaataaaa raaaaacaaa tgtaattgaa atagcacaca gcattctcta    474
gtcaatatct ttagtgatct tctttaataa acatgaaagc aaaaaaaaaa aa            526
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<212> PRT
<213> Homo Sapiens
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<223> SIGNAL
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<223> Von Heijne matrix
      score 8.2
      seq LLLITAILAVAVG/FP
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Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
1               5                   10                  15
Gly
<210> 19
<211> 822
<212> DNA
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ctgatgccga gttccgtctc tcgcgtcttt tcctggtccc aggcaaagcg gasgnagatc 120
ctcaaacggc ctagtgcttc gcgcttccgg agaaaatcag cggtctaatt aattcctctg 180
gtttgttgaa gcagttacca agaatcttca acccctttccc acaaaagcta attgagtaca 240
cgttcctgtt gagtacacgt tcctgttgat ttacaaaagg tgcaggtatg agcaggtctg 300
aagactaaca ttttgtgaag ttgtaaaaca gaaaaccctgt tagaa atg tgg tgg ttt 357
Met Trp Trp Phe
-20
cag caa ggc ctc agt ttc ctt cct tca gcc ctt gta att tgg aca tct 405
Gln Gln Gly Leu Ser Phe Leu Pro Ser Ala Leu Val Ile Trp Thr Ser
-15 -10 -5
gct gct ttc ata ttt tca tac att act gca gta aca ctc cac cat ata 453
Ala Ala Phe Ile Phe Ser Tyr Ile Thr Ala Val Thr Leu His His Ile
1 5 10 15
gac ccg gct tta cct tat atc agt gac act ggt aca gta gct cca raa 501
Asp Pro Ala Leu Pro Tyr Ile Ser Asp Thr Gly Thr Val Ala Pro Xaa
20 25 30
aaa tgc tta ttt ggg gca atg cta aat att gcg gca gtt tta tgt caa 549
Lys Cys Leu Phe Gly Ala Met Leu Asn Ile Ala Ala Val Leu Cys Gln
35 40 45
aaa tagaaatcag gaaratаatt caacttaaag aakttcattt catgaccaaa 602
Lys
ctcttcaraa acatgtcttt acaagcatat ctcttgtatt gctttctaca ctgttgaatt 662
gtctggcaat atttctgcag tggaaaattt gatttarmta gttcttgact gataaatatg 722
gtaaggtggg cttttccccc tgtgtaattg gctactatgt cttactgagc caagttgtaw 782
tttgaaataa aatgatatga gagtgacaca aaaaaaaaaa 822
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<211> 21
<212> PRT
<213> Homo Sapiens
<220>
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1 5 10 15
Ile Trp Thr Ser Ala
20
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<222> 185..295
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cccagcccaa gtcagccttc agcacgcgct tttctgcaca cagatattcc aggcctacct 120
ggcattccag gacctccgma atgatgctcc agtcccttac aagcgcttcc tggatgaggg 180
tggc atg gtg ctg acc acc ctc ccc ttg ccc tct gcc aac agc cct gtg 229
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val
-35 -30 -25
aac atg ccc acc act ggc ccc aac agc ctg agt tat gct agc tct gcc 277

```
Asn Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala
        -20                 -15                 -10
ctg tcc ccc tgt ctg acc gct cca aak tcc ccc cgg ctt gct atg atg      325
Leu Ser Pro Cys Leu Thr Ala Pro Xaa Ser Pro Arg Leu Ala Met Met
    -5                  1               5                   10
cct gac aac taaatatcct tatccaaatc aataaarwra raatcctccc            374
Pro Asp Asn
tccaraaggg tttctaaaaa caaaaaaaaa a                                 405
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<212> PRT
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<222> 1..37
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      score 5.9
      seq LSYASSALSPCLT/AP
<400> 22
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
1               5                   10                  15
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
            20                  25                  30
Ser Pro Cys Leu Thr
        35
<210> 23
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attagccgtg gcctaggccg tttaacgggg tgacacgagc ntgcagggcc gagtccaagg   120
cccggagata ggaccaaccg tcaggaatgc gaggaatgtt tttcttcgga ctctatcgag   180
gcacacagac agacc atg ggg att ctg tct aca gtg aca gcc tta aca ttt     231
               Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe
               -15                 -10                 -5
gcc ara gcc ctg gac ggc tgc aga aat ggc att gcc cac cct gca agt      279
Ala Xaa Ala Leu Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser
            1               5                   10
gag aag cac aga ctc gag aaa tgt agg gaa ctc gag asc asc cac tcg      327
Glu Lys His Arg Leu Glu Lys Cys Arg Glu Leu Glu Xaa Xaa His Ser
    15                  20                  25
gcc cca gga tca acc cas cac cga aga aaa aca acc aga aga aat tat      375
Ala Pro Gly Ser Thr Xaa His Arg Arg Lys Thr Thr Arg Arg Asn Tyr
30                  35                  40                  45
tct tca gcc tgaaatgaak ccgggatcaa atggttgctg atcaragccc             424
Ser Ser Ala
atatttaaat tggaaaagtc aaattgasca ttattaaata aagcttgttt aatatgtctc   484
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aaacaaaaaa aa                                                          496
<210> 24
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<222> 1..15
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      score 5.5
      seq ILSTVTALTFAXA/LD
<400> 24
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Xaa Ala
1               5                   10                  15
<210> 25
<211> 623
<212> DNA
<213> Homo Sapiens
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<223> sig_peptide
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aaagatccct gcagcccggc aggagagaag gctgagcctt ctggcgtc atg gag agg       57
                                                    Met Glu Arg
                                                     -15
ctc gtc cta acc ctg tgc acc ctc ccg ctg gct gtg gcg tct gct ggc       105
Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly
            -10                 -5                  1
tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag       153
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
    5                   10                  15
gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac       201
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp
20                  25                  30                  35
caa gtc tgc atc tcc aac gag gtg gtc gtc tct ttt aaa tgg agt gta       249
Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys Trp Ser Val
                40                  45                  50
cgc gtc ctg ctc agc aaa cgc tgt gct ccc aga tgt ccc aac gac aac       297
Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro Asn Asp Asn
            55                  60                  65
atg aak ttc gaa tgg tcg ccg gcc ccc atg gtg caa ggc gtg atc acc       345
Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly Val Ile Thr
        70                  75                  80
agg cgc tgc tgt tcc tgg gct ctc tgc aac agg gca ctg acc cca cag       393
Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu Thr Pro Gln
    85                  90                  95
gag ggg cgc tgg gcc ctg cra ggg ggg ctc ctg ctc cag gac cct tcg       441
Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln Asp Pro Ser
100                 105                 110                 115
agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc       489
Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys
                120                 125                 130
ctt ccc awt tcc aac ccc ctc tgc cca rgg gaa acc cag gaa gga            534
Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln Glu Gly
            135                 140                 145
taacactgtg ggtgccccca cctgtgcatt gggaccacra cttcaccctc ttggaracaa      594
taaactctca tgcccccaaa aaaaaaaaa                                        623
<210> 26
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<220>
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<222> 1..16
<223> Von Heijne matrix
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seq LVLTLCTLPLAVA/SA
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1               5                  10                  15
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                                                  -10
ctg gtg act gcc att cat gct gaa ctc tgt caa cca ggt gca gaa aat       100
Leu Val Thr Ala Ile His Ala Glu Leu Cys Gln Pro Gly Ala Glu Asn
        -5                  1               5
gct ttt aaa gtg aga ctt agt atc aga aca gct ctg gga gat aaa gca       148
Ala Phe Lys Val Arg Leu Ser Ile Arg Thr Ala Leu Gly Asp Lys Ala
10                  15                  20                  25
tat gcc tgg gat acc aat gaa gaa tac ctc ttc aaa gcg atg gta gct       196
Tyr Ala Trp Asp Thr Asn Glu Glu Tyr Leu Phe Lys Ala Met Val Ala
                30                  35                  40
ttc tcc atg aga aaa gtt ccc aac aga gaa gca aca gaa att tcc cat       244
Phe Ser Met Arg Lys Val Pro Asn Arg Glu Ala Thr Glu Ile Ser His
            45                  50                  55
gtc cta ctt tgc aat gta acc cag agg gta tca ttc tgg ttt gtg gtt       292
Val Leu Leu Cys Asn Val Thr Gln Arg Val Ser Phe Trp Phe Val Val
        60                  65                  70
aca gac cct tca aaa aat cac acc ctt cct gct gtt gag gtg caa tca       340
Thr Asp Pro Ser Lys Asn His Thr Leu Pro Ala Val Glu Val Gln Ser
    75                  80                  85
gcc ata aga atg aac aag aac cgg atc aac aat gcc ttc ttt cta aat       388
Ala Ile Arg Met Asn Lys Asn Arg Ile Asn Asn Ala Phe Phe Leu Asn
90                  95                  100                 105
gac caa act ctg gaa ttt tta aaa atc cct tcc aca ctt gca cca ccc       436
Asp Gln Thr Leu Glu Phe Leu Lys Ile Pro Ser Thr Leu Ala Pro Pro
                110                 115                 120
atg gac cca tct gtg ccc atc tgg att att ata ttt ggt gtg ata ttt       484
Met Asp Pro Ser Val Pro Ile Trp Ile Ile Ile Phe Gly Val Ile Phe
            125                 130                 135
tgc atc atc ata gtt gca att gca cta ctg att tta tca ggg atc tgg       532
Cys Ile Ile Ile Val Ala Ile Ala Leu Leu Ile Leu Ser Gly Ile Trp
        140                 145                 150
caa cgt ada ara aag aac aaa gaa cca tct gaa gtg gat gac gct gaa       580
Gln Arg Xaa Xaa Lys Asn Lys Glu Pro Ser Glu Val Asp Asp Ala Glu
    155                 160                 165
rat aak tgt gaa aac atg atc aca att gaa aat ggc atc ccc tct gat       628
Xaa Xaa Cys Glu Asn Met Ile Thr Ile Glu Asn Gly Ile Pro Ser Asp
170                 175                 180                 185
ccc ctg gac atg aag gga ggg cat att aat gat gcc ttc atg aca gag       676
Pro Leu Asp Met Lys Gly Gly His Ile Asn Asp Ala Phe Met Thr Glu
                190                 195                 200
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gat gag agg ctc acc cct ctc tgaagggctg ttgttctgct tcctcaaraa 727
Asp Glu Arg Leu Thr Pro Leu
205
attaaacatt tgtttctgtg tgactgctga gcatcctgaa ataccaagag cagatcatat 787
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score 0.983
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score 0.961
sequence cccaactgac
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name S8_01
score 0.960

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sequence agataaatcca
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score 0.954
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sequence agttgggaattc
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score 0.962
sequence cctgggga
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score 0.994
sequence tgaccgttg
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name STAT_01
score 0.951
sequence ttccaggaa
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name USF_01
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score 0.956

sequence cagcacgtgagt
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name MYCMAX_02
score 0.972
sequence cagcacgtgagt
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name USF_C
score 0.997
sequence tcacgtgc
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name USF_C
score 0.991
sequence gcacgtga
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score 0.968
sequence catgggga
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name ELK1_02
score 0.963
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score 0.961
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kawaagctca gcaccggtgc ccatcacagg gccggcagca cacacatccc attactcaga 180
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cattcctgtc tgcattagta actcccaacc tagatgtgaa aacttagttc tttctcatag 360
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cgtgtcttct gcctgctccc gctcacatcc cacacttgtg ttcagtcact gagttacaga 480
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score 10.7
seq LLTLALLGGPTWA/GK
<223> polyA_signal
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<223> polyA_site
<222> 685..699
<400> 40

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aaccagacgc ccagtcacag gcgagagccc tggg atg cac cgg cca gag gcc atg      55
                                      Met His Arg Pro Glu Ala Met
                                          -20
ctg ctg ctg ctc acg ctt gcc ctc ctg ggg ggc ccc acc tgg gca ggg      103
Leu Leu Leu Leu Thr Leu Ala Leu Leu Gly Gly Pro Thr Trp Ala Gly
-15                 -10                 -5                  1
aag atg tat ggc cct gga gga ggc aag tat ttc agc acc act gaa gac      151
Lys Met Tyr Gly Pro Gly Gly Gly Lys Tyr Phe Ser Thr Thr Glu Asp
            5                   10                  15
tac gac cat gaa atc aca ggg ctg cgg gtg tct gta ggt ctt ctc ctg      199
Tyr Asp His Glu Ile Thr Gly Leu Arg Val Ser Val Gly Leu Leu Leu
        20                  25                  30
gtg aaa agt gtc cag gtg aaa ctt gga gac tcc tgg gac gtg aaa ctg      247
Val Lys Ser Val Gln Val Lys Leu Gly Asp Ser Trp Asp Val Lys Leu
    35                  40                  45
gga gcc tta ggt ggg aat acc cag gaa gtc acc ctg cag cca ggc gaa      295
Gly Ala Leu Gly Gly Asn Thr Gln Glu Val Thr Leu Gln Pro Gly Glu
50                  55                  60                  65
tac atc aca aaa gtc ttt gtc gcc ttc caa act ttc ctc cgg ggt atg      343
Tyr Ile Thr Lys Val Phe Val Ala Phe Gln Thr Phe Leu Arg Gly Met
                70                  75                  80
gtc atg tac acc agc aag gac cgc tat ttc tat ttt ggg aag ctt gat      391
Val Met Tyr Thr Ser Lys Asp Arg Tyr Phe Tyr Phe Gly Lys Leu Asp
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            85                  90                  95
ggc cag atc tcc tct gcc tac ccc agc caa gag ggg cag gtg ctg gtg      439
Gly Gln Ile Ser Ser Ala Tyr Pro Ser Gln Glu Gly Gln Val Leu Val
        100                 105                 110
ggc atc tat ggc cag tat caa ctc ctt ggc atc aag agc att ggc ttt      487
Gly Ile Tyr Gly Gln Tyr Gln Leu Leu Gly Ile Lys Ser Ile Gly Phe
    115                 120                 125
gaa tgg aat tat cca cta gag gag ccg acc act gag cca cca gtt aat      535
Glu Trp Asn Tyr Pro Leu Glu Glu Pro Thr Thr Glu Pro Pro Val Asn
130                 135                 140                 145
ctc aca tac tca gca aac tca ccc gtg ggt cgc tagggtgggg tatggggcca     588
Leu Thr Tyr Ser Ala Asn Ser Pro Val Gly Arg
                150                 155
tccgagctga ggccatctgg gtggtggtgg ctgatggtac tggagtaact gagtcgggac     648
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<223> polyA_site
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caccacc atg aag ttc tta gca gtc ctg gta ctc ttg gga gtt tcc atc      109
        Met Lys Phe Leu Ala Val Leu Val Leu Leu Gly Val Ser Ile
                    -15                 -10
ttt ctg gtc tct gcc cag aat ccg aca aca gct gct cca gct gac acg      157
Phe Leu Val Ser Ala Gln Asn Pro Thr Thr Ala Ala Pro Ala Asp Thr
-5                  1                   5                   10
tat cca gct act ggt cct gct gat gat gaa gcc cct gat gct gaa acc      205
Tyr Pro Ala Thr Gly Pro Ala Asp Asp Glu Ala Pro Asp Ala Glu Thr
            15                  20                  25
act gct gct gca acc act gcg acc act gct gct cct acc act gca acc      253
Thr Ala Ala Ala Thr Thr Ala Thr Thr Ala Ala Pro Thr Thr Ala Thr
        30                  35                  40
acc gct gct tct acc act gct cgt aaa gac att cca gtt tta ccc aaa      301
Thr Ala Ala Ser Thr Thr Ala Arg Lys Asp Ile Pro Val Leu Pro Lys
    45                  50                  55
tgg gtt ggg gat ctc ccg aat ggt aga gtg tgt ccc tgagatggaa           347
Trp Val Gly Asp Leu Pro Asn Gly Arg Val Cys Pro
60                  65                  70
tcagcttgag tcttctgcaa ttggtcacaa ctattcatgc ttcctgtgat ttcatccaac     407
tacttacctt gcctacgata tccccttttat ctctaatcag tttatttttct ttcaaataaa     467
aaataactat gagcaaaaaa aaaaaaaaaa                                      497
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<222> 583..598
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aat ctg ctg agc tcg cat gtg cgg ggg gtg ggg tcc cgt ggc ttc ccc 104
Asn Leu Leu Ser Ser His Val Arg Gly Val Gly Ser Arg Gly Phe Pro
-5 1 5
ctg cgc ctc cag gcc acc gag gtc cgt atc tgc cct gtg gaa ttc aac 152
Leu Arg Leu Gln Ala Thr Glu Val Arg Ile Cys Pro Val Glu Phe Asn
10 15 20
ccc aac ttc gtg gcg cgt atg ata cct aaa gtg gag tgg tcg gcg ttc 200
Pro Asn Phe Val Ala Arg Met Ile Pro Lys Val Glu Trp Ser Ala Phe
25 30 35
ctg gag gcg gcc gat aac ttg cgt ctg atc cag gtg ccg aaa ggg ccg 248
Leu Glu Ala Ala Asp Asn Leu Arg Leu Ile Gln Val Pro Lys Gly Pro
40 45 50 55
gtt gag gga tat gag gag aat gag gag ttt ctg agg acc atg cac cac 296
Val Glu Gly Tyr Glu Glu Asn Glu Glu Phe Leu Arg Thr Met His His
60 65 70
ctg ctg ctg gag gtg gaa gtg ata gag ggc acc ctg cag tgc ccg gaa 344
Leu Leu Leu Glu Val Glu Val Ile Glu Gly Thr Leu Gln Cys Pro Glu
75 80 85
tct gga cgt atg ttc ccc atc agc cgc ggg atc ccc aac atg ctg ctg 392
Ser Gly Arg Met Phe Pro Ile Ser Arg Gly Ile Pro Asn Met Leu Leu
90 95 100
agt gaa gag gaa act gag agt tgattgtgcc aggcgccagt ttttcttgtt 443
Ser Glu Glu Glu Thr Glu Ser
105 110
atgactgtgt atttttgttg atctataccc tgtttccgaa ttctgccgtg tgtatcccca 503
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score 8.7
seq HLLALLVFSVLLA/LR
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<222> 1540..1545
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ctgcctctcg ctcgcagcag cggcggcagg cgcgggcgag ggccacgggg agaggagacg 180
cagccccgcg ggtggcacgc tcggccgggc cccggcccgc gctcaacggg cgcg atg 237

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                                                                  Met
ctc ttc tcg ctc cgg gag ctg gtg cag tgg cta ggc ttc gcc acc ttc      285
Leu Phe Ser Leu Arg Glu Leu Val Gln Trp Leu Gly Phe Ala Thr Phe
            -30                 -25                 -20
gag atc ttc gtg cac ctg ctg gcc ctg ttg gtg ttc tct gtg ctg ctg      333
Glu Ile Phe Val His Leu Leu Ala Leu Leu Val Phe Ser Val Leu Leu
        -15                 -10                 -5
gca ctg cgt gtg gat ggc ctg gtc ccg ggc ctc tcc tgg tgg aac gtg      381
Ala Leu Arg Val Asp Gly Leu Val Pro Gly Leu Ser Trp Trp Asn Val
    1               5                   10                  15
ttc gtg cct ttc ttc gcc gct gac ggg ctc agc acc tac ttc acc acc      429
Phe Val Pro Phe Phe Ala Ala Asp Gly Leu Ser Thr Tyr Phe Thr Thr
                20                  25                  30
atc gtg tcc gtg cgc ctc ttc cag gat gga gag aag cgg ctg gcg gtg      477
Ile Val Ser Val Arg Leu Phe Gln Asp Gly Glu Lys Arg Leu Ala Val
            35                  40                  45
ctc cgc ctt ttc tgg gta ctt acg gtc ctg agt ctc aag ttc gtc ttc      525
Leu Arg Leu Phe Trp Val Leu Thr Val Leu Ser Leu Lys Phe Val Phe
        50                  55                  60
gag atg ctg ttg tgc cag aag ctg gcg gag cag act cgg gag ctc tgg      573
Glu Met Leu Leu Cys Gln Lys Leu Ala Glu Gln Thr Arg Glu Leu Trp
    65                  70                  75
ttc ggc ctc att acg tcc ccg ctc ttc att ctc ctg cag ctg ctc atg      621
Phe Gly Leu Ile Thr Ser Pro Leu Phe Ile Leu Leu Gln Leu Leu Met
80                  85                  90                  95
atc cgc gcc tgt cgg gtc aac tagcctcacc gaggtgccgg agagggagcg          672
Ile Arg Ala Cys Arg Val Asn
                100
ctggacaact agaatgttga cctcgagccg aggccctact tgcagcgcac cggaggagag    732
gctctctagt ctgaaggcac cgccggcttg cgccgagctg agtgccgggt ttccctattc    792
caatcctgtt tgaaatggtt tcttcagcag ggcttaaaag agcagccttc atcctgaaaa    852
tgtatttcct tttgtttaat gctttgagta gataatcctg aattgaggtc atgaggaggc    912
cccccaggcc agacagtcct gaacccctct gacacttgga aactgaatat aagtaaaatg    972
tccaggtgga ctctgagtat ttcctgtgga tcctgggaaa gtactgttgc acaaaggctg   1032
caaagctgga ctcaggaatg tcctccaacc agcagcgcta acctaagagc tccctgtgcc   1092
gtctatccag accagacttc ggtagatgcc tttgttagat ctatcacatg taaacgagct   1152
tgtatctcct tccctgtgcc acgagagaga ttggcttttt attccagtct aggcagagac   1212
agaagaatgt tgaataagag cacgattaga gtcctgtctg gttatctgtt gcccaagaaa   1272
agaactctgc tgtccaggca ctgcttggct tactatccca gcaaagactg cagttttgtg   1332
gacttttgac caccttgggc tggcactctt agcacacctg agacagattt aagcctccct   1392
aagagactga agagaggaac aggtgtcaga tactcatagg cactgagatc tacaaatggg   1452
aagcttgtga gtggcccatc tttgttggcc tacgaacttt ggtttgatgc cagtcaggtg   1512
ccacatgaga acctttgctg agatgcaaat aaagtaagag aatgttttcc caaaaaaaaa   1572
aaaaaaa                                                            1579
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<223> Von Heijne matrix
      score 5.8
      seq ILSLQVLLTTVTS/TV
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<223> polyA_site
<222> 878..893
<400> 44
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gcggttagtg gaccgggacc ggtaggggtg ctgttgccat c atg gct gac ccc gac      56
                                              Met Ala Asp Pro Asp
                                                             -50
ccc cgg tac cct cgc tcc tcg atc gag gac gac ttc aac tat ggc agc      104
Pro Arg Tyr Pro Arg Ser Ser Ile Glu Asp Asp Phe Asn Tyr Gly Ser
            -45                 -40                 -35
agc gtg gcc tcc gcc acc gtg cac atc cga atg gcc ttt ctg aga aaa      152
Ser Val Ala Ser Ala Thr Val His Ile Arg Met Ala Phe Leu Arg Lys
        -30                 -25                 -20
gtc tac agc att ctt tct ctg cag gtt ctc tta act aca gtg act tca      200
Val Tyr Ser Ile Leu Ser Leu Gln Val Leu Leu Thr Thr Val Thr Ser
    -15                 -10                 -5
aca gtt ttt tta tac ttt gag tct gta cgg aca ttt gta cat gag agt      248
Thr Val Phe Leu Tyr Phe Glu Ser Val Arg Thr Phe Val His Glu Ser
1               5                   10                  15
cct gcc tta att ttg ctg ttt gcc ctc gga tct ctg ggt ttg att ttt      296
Pro Ala Leu Ile Leu Leu Phe Ala Leu Gly Ser Leu Gly Leu Ile Phe
            20                  25                  30
gcg ttg att tta aac aga cat aag tat ccc ctt aac ctg tac cta ctt      344
Ala Leu Ile Leu Asn Arg His Lys Tyr Pro Leu Asn Leu Tyr Leu Leu
        35                  40                  45
ttt gga ttt acg ctg ttg gaa gct ctg act gtg gca gtt gtt gtt act      392
Phe Gly Phe Thr Leu Leu Glu Ala Leu Thr Val Ala Val Val Val Thr
    50                  55                  60
ttc tat gat gta tat att att ctg caa gct ttc ata ctg act act aca      440
Phe Tyr Asp Val Tyr Ile Ile Leu Gln Ala Phe Ile Leu Thr Thr Thr
65                  70                  75                  80
gta ttt ttt ggt ttg act gtg tat act cta caa tct aag aag gat ttc      488
Val Phe Phe Gly Leu Thr Val Tyr Thr Leu Gln Ser Lys Lys Asp Phe
                85                  90                  95
agc aaa ttt gga gca ggg ctg ttt gct ctt ttg tgg ata ttg tgc ctg      536
Ser Lys Phe Gly Ala Gly Leu Phe Ala Leu Leu Trp Ile Leu Cys Leu
            100                 105                 110
tca gga ttc ttg aag ttt ttt tta tat agt gag ata atg gag ttg gtc      584
Ser Gly Phe Leu Lys Phe Phe Leu Tyr Ser Glu Ile Met Glu Leu Val
        115                 120                 125
tta gcc gct gca gga gcc ctt ctt ttc tgt gga ttc atc atc tat gac      632
Leu Ala Ala Ala Gly Ala Leu Leu Phe Cys Gly Phe Ile Ile Tyr Asp
    130                 135                 140
aca cac tca ctg atg cat aaa ctg tca cct gaa gag tac gta tta gct      680
Thr His Ser Leu Met His Lys Leu Ser Pro Glu Glu Tyr Val Leu Ala
145                 150                 155                 160
gcc atc agc ctc tac ttg gat atc atc aat cta ttc ctg cac ctg tta      728
Ala Ile Ser Leu Tyr Leu Asp Ile Ile Asn Leu Phe Leu His Leu Leu
                165                 170                 175
cgg ttt ctg gaa gca gtt aat aaa aag taattaaaag tatctcagct             775
Arg Phe Leu Glu Ala Val Asn Lys Lys
            180                 185
caactgaaga acaacaaaaa aaatttaacg agaaaaaagg attaaagtaa ttggaagcag     835
tatatagaaa ctgtttcatt aagtaataaa gtttgaacca ataaaaaaaa aaaaaaaa       893
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<223> Von Heijne matrix
      score 3.9
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                        Met Ser Thr Asn Asn Met Ser Asp Pro Arg
                           -70                 -65
agg ccg aac aaa gtg ctg agg tac aag ccc ccg ccg agc gaa tgt aac      100
Arg Pro Asn Lys Val Leu Arg Tyr Lys Pro Pro Pro Ser Glu Cys Asn
    -60                 -55                 -50
ccg gcc ttg gac gac ccg acg ccg gac tac atg aac ctg ctg ggc atg      148
Pro Ala Leu Asp Asp Pro Thr Pro Asp Tyr Met Asn Leu Leu Gly Met
-45                 -40                 -35                 -30
atc ttc agc atg tgc ggc ctc atg ctt aag ctg aag tgg tgt gct tgg      196
Ile Phe Ser Met Cys Gly Leu Met Leu Lys Leu Lys Trp Cys Ala Trp
                -25                 -20                 -15
gtc gct gtc tac tgc tcc ttc atc agc ttt gcc aac tct cgg agc tcg      244
Val Ala Val Tyr Cys Ser Phe Ile Ser Phe Ala Asn Ser Arg Ser Ser
            -10                 -5                  1
gag gac acg aag caa atg atg agt agc ttc atg ctg tcc atc tct gcc      292
Glu Asp Thr Lys Gln Met Met Ser Ser Phe Met Leu Ser Ile Ser Ala
    5                   10                  15
gtg gtg atg tcc tat ctg cag aat cct cag ccc atg acg ccc cca tgg      340
Val Val Met Ser Tyr Leu Gln Asn Pro Gln Pro Met Thr Pro Pro Trp
20                  25                  30                  35
tgataccagc ctagaagggt cacattttgg accctgtcta tccactaggc ctgggctttg    400
gctgctaaac ctgctgcctt cagctgccat cctggacttc cctgaatgag gccgtctcgg    460
tgccccccagc tggatagagg gaacctggcc ctttcctagg gaacacccta ggcttacccc   520
tcctgcctcc cttcccctgc ctgctgctgg gggagatgct gtccatgttt ctaggggtat    580
tcatttgctt tctcgttgaa acctgttgtt aataaagttt ttcactctaa aaaaaaaaaa    640
aaaa                                                                644
<210> 46
<211> 538
<212> DNA
<213> Homo sapiens
<220>
<223> CDS
<222> 12..380
<223> sig_peptide
<222> 12..263
<223> Von Heijne matrix
      score 6.2
      seq GLFRAAWLPGSRP/SP
<223> polyA_site
<222> 523..538
<400> 46
ctgaattcct t atg tcc ggt ggg cca gaa gcc cgt cct cct atg ctg gtg      50
             Met Ser Gly Gly Pro Glu Ala Arg Pro Pro Met Leu Val
                            -80                 -75
gaa ggc gga gga ccg gag tcc ctg cag aag gcc ccg tgc act cgg ggg       98
Glu Gly Gly Gly Pro Glu Ser Leu Gln Lys Ala Pro Cys Thr Arg Gly
    -70                 -65                 -60
cct ccc tca cat ccc gtg ccc cct gcg ctg gcc ttc aca gta ggt aat      146
Pro Pro Ser His Pro Val Pro Pro Ala Leu Ala Phe Thr Val Gly Asn
-55                 -50                 -45                 -40
ggc tcc ggc ccg ggt gtt cgc tgt cca cgg aac atg gca gag ggg cac      194
Gly Ser Gly Pro Gly Val Arg Cys Pro Arg Asn Met Ala Glu Gly His
                -35                 -30                 -25
ccc ggc ccg gaa aga cgc cag agc cag cag ggg ctg ttt cgg gcc gcg      242
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Pro Gly Pro Glu Arg Arg Gln Ser Gln Gln Gly Leu Phe Arg Ala Ala
           -20                 -15                 -10
tgg ctc ccc ggg tct cgg ccg tct ccc ctc ttc tgc gtc tgt tcc gtg      290
Trp Leu Pro Gly Ser Arg Pro Ser Pro Leu Phe Cys Val Cys Ser Val
       -5                  1                   5
act tcg cct ggg tgg gat gta ccg cag gtg cat cgc gtc gag gtg ggg      338
Thr Ser Pro Gly Trp Asp Val Pro Gln Val His Arg Val Glu Val Gly
10                 15                  20                  25
cac ggc cgc cgg caa gaa acc cac cct gtc cgg agg cgg gcg              380
His Gly Arg Arg Gln Glu Thr His Pro Val Arg Arg Arg Ala
                30                  35
tgagacaagc ccagcccgca cgcgctcatc tttcttcgtt ttttgatcag tttattcaga    440
attgctctat aatttaccaa ttgtatgtat ttaacctatt cttgtggaaa aaaaaggtct    500
ttcattatat ctttatttct gcaaaaaaaa aaaaaaaa                            538
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<211> 752
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<222> 8..232
<223> sig_peptide
<222> 8..154
<223> Von Heijne matrix
      score 4.7
      seq DTFLLSFLSTTWL/KT
<223> polyA_site
<222> 737..752
<400> 47
gggggtg atg ccg cgc ggt cgc agg ctt ggg atg gtg ttc gcg cct ccg       49
        Met Pro Arg Gly Arg Arg Leu Gly Met Val Phe Ala Pro Pro
                    -45                 -40
aga ccc gga cag agg caa gca ggg gcg ccg tgg gtg cca gag agg cgg       97
Arg Pro Gly Gln Arg Gln Ala Gly Ala Pro Trp Val Pro Glu Arg Arg
-35                 -30                 -25                 -20
aag agg agg cct gat ggg gat acc ttc ctg ctg tcc ttc ctg agc aca      145
Lys Arg Arg Pro Asp Gly Asp Thr Phe Leu Leu Ser Phe Leu Ser Thr
                -15                 -10                 -5
acc tgg ctg aaa acc tgg agg tca caa cag tac aaa gaa tca aag tca      193
Thr Trp Leu Lys Thr Trp Arg Ser Gln Gln Tyr Lys Glu Ser Lys Ser
            1               5                   10
aga tct tgt gcc aga gag caa atg aac tct tcc tct tgc tgagaaaacc       242
Arg Ser Cys Ala Arg Glu Gln Met Asn Ser Ser Ser Cys
    15                  20                  25
caccctgctc acctaaaccc tggccttgcc tggtaattcc atccatgcgc ctggaaggcc    302
ccagacatca aggctctgag gggccaggca cggggagaac ccagcagtgc cctgccctgc    362
agtctgagct accagattcc ttgtgaagat aatttgagga ccatgactca cccaaccaca    422
tttcctgggg cctcaaattg aaaattcagg atgggctttt ctatatgact ggctgatatc    482
caactatgcc atggtcttta catgccatga acattctttc ctgccagagt tctaagaatc    542
tgtgttctct gccttagacc ttctgcagat gagcccacag gaagctccac gtgtagctga    602
gctacatgca ccaggcctca gtttgcccca agtcccctgt gtactctctc atggcctgtg    662
gccaagaaat gtattctctc actttggact taggagtcca aagagaagcc cagaaacaaa    722.
attgcttgaa cttgaaaaaa aaaaaaaaaa                                     752
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<211> 537
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<222> 183..422
<223> sig_peptide
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<222> 183..302
<223> Von Heijne matrix
score 5.8
seq VLFALFVAFLLRG/KL
<223> polyA_signal
<222> 505..510
<223> polyA_site
<222> 523..537
<400> 48
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tgttctcttt caaaattacc aacatggacc ccacccaatt cttcccttgg aactaaggaa 120
cgcctgactg atcatctgat acagcagttc ctgagcagaa caaaacaaca aaaacaggac 180
ag atg gat gga ata ccc atg tca atg aag aat gaa atg ccc atc tcc 227
Met Asp Gly Ile Pro Met Ser Met Lys Asn Glu Met Pro Ile Ser
-40 -35 -30
caa cta ctg atg atc atc gcc ccc tcc ttg gga ttt gtg ctc ttc gca 275
Gln Leu Leu Met Ile Ile Ala Pro Ser Leu Gly Phe Val Leu Phe Ala
-25 -20 -15 -10
ttg ttt gtg gcg ttt ctc ctg aga ggg aaa ctc atg gaa acc tat tgt 323
Leu Phe Val Ala Phe Leu Leu Arg Gly Lys Leu Met Glu Thr Tyr Cys
-5 1 5
tcg cag aaa cac aca agg cta gac tac att gga gat agt aaa aat gtc 371
Ser Gln Lys His Thr Arg Leu Asp Tyr Ile Gly Asp Ser Lys Asn Val
10 15 20
ctc aat gac gtg cag cat gga agg gaa gac gaa gac ggc ctt ttt acc 419
Leu Asn Asp Val Gln His Gly Arg Glu Asp Glu Asp Gly Leu Phe Thr
25 30 35
ctc taacaacgca gtagcatgtt agattgagga tgggggcatg acactccagt 472
Leu
40
gtcaaaataa gtcttagtag atttccttgt ttcataaaaa agactcactc aaaaaaaaaa 532
aaaaa 537
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<222> 24..1004
<223> sig_peptide
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<223> Von Heijne matrix
score 5.6
seq ACLSLGFFSLLWL/QL
<223> polyA_site
<222> 1586..1602
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atgcgccgcc gcctctccgc acg atg ttc ccc tcg cgg agg aaa gcg gcg cag 53
Met Phe Pro Ser Arg Arg Lys Ala Ala Gln
-45 -40
ctg ccc tgg gag gac ggc agg tcc ggg ttg ctc tcc ggc ggc ctc cct 101
Leu Pro Trp Glu Asp Gly Arg Ser Gly Leu Leu Ser Gly Gly Leu Pro
-35 -30 -25
cgg aag tgt tcc gtc ttc cac ctg ttc gtg gcc tgc ctc tcg ctg ggc 149
Arg Lys Cys Ser Val Phe His Leu Phe Val Ala Cys Leu Ser Leu Gly
-20 -15 -10
ttc ttc tcc cta ctc tgg ctg cag ctc agc tgc tct ggg gac gtg gcc 197
Phe Phe Ser Leu Leu Trp Leu Gln Leu Ser Cys Ser Gly Asp Val Ala
-5 1 5
cgg gca gtc agg gga caa ggg cag gag acc tcg ggc cct ccc cgt gcc 245
Arg Ala Val Arg Gly Gln Gly Gln Glu Thr Ser Gly Pro Pro Arg Ala

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10                  15                  20                  25
tgc ccc cca gag ccg ccc cct gag cac tgg gaa gaa gac gca tcc tgg      293
Cys Pro Pro Glu Pro Pro Pro Glu His Trp Glu Glu Asp Ala Ser Trp
                30                  35                  40
ggc ccc cac cgc ctg gca gtg ctg gtg ccc ttc cgc gaa cgc ttc gag      341
Gly Pro His Arg Leu Ala Val Leu Val Pro Phe Arg Glu Arg Phe Glu
            45                  50                  55
gag ctc ctg gtc ttc gtg ccc cac atg cgc cgc ttc ctg agc agg aag      389
Glu Leu Leu Val Phe Val Pro His Met Arg Arg Phe Leu Ser Arg Lys
        60                  65                  70
aag atc cgg cac cac atc tac gtg ctc aac cag gtg gac cac ttc agg      437
Lys Ile Arg His His Ile Tyr Val Leu Asn Gln Val Asp His Phe Arg
    75                  80                  85
ttc aac cgg gca gcg ctc atc aac gtg ggc ttc ctg gag agc agc aac      485
Phe Asn Arg Ala Ala Leu Ile Asn Val Gly Phe Leu Glu Ser Ser Asn
90                  95                  100                 105
agc acg gac tac att gcc atg cac gac gtt gac ctg ctc cct ctc aac      533
Ser Thr Asp Tyr Ile Ala Met His Asp Val Asp Leu Leu Pro Leu Asn
                110                 115                 120
gag gag ctg gac tat ggc ttt cct gag gct ggg ccc ttc cac gtg gcc      581
Glu Glu Leu Asp Tyr Gly Phe Pro Glu Ala Gly Pro Phe His Val Ala
            125                 130                 135
tcc ccg gag ctc cac cct ctc tac cac tac aag acc tat gtc ggc ggc      629
Ser Pro Glu Leu His Pro Leu Tyr His Tyr Lys Thr Tyr Val Gly Gly
        140                 145                 150
atc ctg ctg ctc tcc aag cag cac tac cgg ctg tgc aat ggg atg tcc      677
Ile Leu Leu Leu Ser Lys Gln His Tyr Arg Leu Cys Asn Gly Met Ser
    155                 160                 165
aac cgc ttc tgg ggc tgg ggc cgc gag gac gac gag ttc tac cgg cgc      725
Asn Arg Phe Trp Gly Trp Gly Arg Glu Asp Asp Glu Phe Tyr Arg Arg
170                 175                 180                 185
att aag gga gct ggg ctc cag ctt ttc cgc ccc tcg gga atc aca act      773
Ile Lys Gly Ala Gly Leu Gln Leu Phe Arg Pro Ser Gly Ile Thr Thr
                190                 195                 200
ggg tac aag aca ttt cgc cac ctg cat gac cca gcc tgg cgg aag agg      821
Gly Tyr Lys Thr Phe Arg His Leu His Asp Pro Ala Trp Arg Lys Arg
            205                 210                 215
gac cag aag cgc atc gca gct caa aaa cag gag cag ttc aag gtg gac      869
Asp Gln Lys Arg Ile Ala Ala Gln Lys Gln Glu Gln Phe Lys Val Asp
        220                 225                 230
agg gag gga ggc ctg aac act gtg aag tac cat gtg gct tcc cgc act      917
Arg Glu Gly Gly Leu Asn Thr Val Lys Tyr His Val Ala Ser Arg Thr
    235                 240                 245
gcc ctg tct gtg ggc ggg gcc ccc tgc act gtc ctc aac atc atg ttg      965
Ala Leu Ser Val Gly Gly Ala Pro Cys Thr Val Leu Asn Ile Met Leu
250                 255                 260                 265
gac tgt gac aag acc gcc aca ccc tgg tgc aca ttc agc tgagctggat      1014
Asp Cys Asp Lys Thr Ala Thr Pro Trp Cys Thr Phe Ser
                270                 275
ggacagtgag gaagcctgta cctacaggcc atattgctca ggctcaggac aaggcctcag   1074
gtcgtgggcc cagctctgac aggatgtgga gtggccagga ccaagacagc aagctacgca   1134
attgcagcca cccggccgcc aaggcaggct tgggctgggc caggacacgt ggggtgcctg   1194
ggacgctgct tgccatgcac agtgatcaga gagaggctgg ggtgtgtcct gtccgggacc   1254
ccccctgcct tcctgctcac cctactctga cctccttcac gtgcccaggc ctgtgggtag   1314
tggggagggc tgaacaggac aacctctcat caccccccact tttgttcctt cctgctgggc  1374
tgcctcgtgc agagacacag tgtaggggcc atgcagctgg cgtaggtggc agttgggcct   1434
ggtgagggtt aggacttcag aaaccagagc acaagcccca cagaggggga acagccagca   1494
ccgctctagc tggttgttgc catgccggaa tgtgggccta gtgttgccag atcttctgat   1554
ttttcgaaag aaactagaat gctggattct caaaaaaaaa aaaaaaaa                 1602
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score 4
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<222> 910..915
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<222> 933..948
<400> 50

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ggggagcggc acctggaag atg cgc cca ttg gct ggt ggc ctg ctc aag gtg      112
                    Met Arg Pro Leu Ala Gly Gly Leu Leu Lys Val
                    -20                 -15                 -10
gtg ttc gtg gtc ttc gcc tcc ttg tgt gcc tgg tat tcg ggg tac ctg      160
Val Phe Val Val Phe Ala Ser Leu Cys Ala Trp Tyr Ser Gly Tyr Leu
                -5                  1               5
ctc gca gag ctc att cca gat gca ccc ctg tcc agt gct gcc tat agc      208
Leu Ala Glu Leu Ile Pro Asp Ala Pro Leu Ser Ser Ala Ala Tyr Ser
        10                  15                  20
atc cgc agc atc ggg gag agg cct gtc ctc aaa gct cca gtc ccc aaa      256
Ile Arg Ser Ile Gly Glu Arg Pro Val Leu Lys Ala Pro Val Pro Lys
    25                  30                  35
agg caa aaa tgt gac cac tgg act ccc tgc cca tct gac acc tat gcc      304
Arg Gln Lys Cys Asp His Trp Thr Pro Cys Pro Ser Asp Thr Tyr Ala
40                  45                  50                  55
tac agg tta ctc agc gga ggt ggc aga agc aag tac gcc aaa atc tgc      352
Tyr Arg Leu Leu Ser Gly Gly Gly Arg Ser Lys Tyr Ala Lys Ile Cys
                60                  65                  70
ttt gag gat aac cta ctt atg gga gaa cag ctg gga aat gtt gcc aga      400
Phe Glu Asp Asn Leu Leu Met Gly Glu Gln Leu Gly Asn Val Ala Arg
            75                  80                  85
gga ata aac att gcc att gtc aac tat gta act ggg aat gtg aca gca      448
Gly Ile Asn Ile Ala Ile Val Asn Tyr Val Thr Gly Asn Val Thr Ala
        90                  95                  100
aca cga tgt ttt gat atg tat gaa ggc gat aac tct gga ccg atg aca      496
Thr Arg Cys Phe Asp Met Tyr Glu Gly Asp Asn Ser Gly Pro Met Thr
    105                 110                 115
aag ttt att cag agt gct gct cca aaa tcc ctg ctc ttc atg gtg acc      544
Lys Phe Ile Gln Ser Ala Ala Pro Lys Ser Leu Leu Phe Met Val Thr
120                 125                 130                 135
tat gac gac gga agc aca aga ctg aat aac gat gcc aag aat gcc ata      592
Tyr Asp Asp Gly Ser Thr Arg Leu Asn Asn Asp Ala Lys Asn Ala Ile
                140                 145                 150
gaa gca ctt gga agt aaa gaa atc agg aac atg aaa ttc agg tct agc      640
Glu Ala Leu Gly Ser Lys Glu Ile Arg Asn Met Lys Phe Arg Ser Ser
            155                 160                 165
tgg gta ttt att gca gca aaa ggc ttg gaa ctc cct tcc gaa att cag      688
Trp Val Phe Ile Ala Ala Lys Gly Leu Glu Leu Pro Ser Glu Ile Gln
        170                 175                 180
aga gaa aag atc aac cac tct gat gct aag aac aac aga tat tct ggc      736
Arg Glu Lys Ile Asn His Ser Asp Ala Lys Asn Asn Arg Tyr Ser Gly
    185                 190                 195
tgg cct gca gag atc cag ata gaa ggc tgc ata ccc aaa gaa cga agc      784
Trp Pro Ala Glu Ile Gln Ile Glu Gly Cys Ile Pro Lys Glu Arg Ser
200                 205                 210                 215
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tgacactgca gggtcctgag taaatgtgtt ctgtataaac aaatgcagct ggaatcgctc    844
aagaatctta tttttctaaa tccaacagcc catatttgat gagtattttg ggtttgttgt    904
aaaccaatga acatttgcta gttgtaccaa aaaaaaaaaa aaaa                     948
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      score 5.8
      seq VLFSASSFPSISG/NI
<223> polyA_site
<222> 673..687
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acaaga atg cgg gtt tat aaa agg aca cag ttg agg caa gag acc gga       108
       Met Arg Val Tyr Lys Arg Thr Gln Leu Arg Gln Glu Thr Gly
           -30                 -25                 -20
ccc aaa agt tat gtg ctc ttt agt gcc tca agt ttt cca agc atc tct      156
Pro Lys Ser Tyr Val Leu Phe Ser Ala Ser Ser Phe Pro Ser Ile Ser
        -15                 -10                 -5
ggt aac ata agg agt aga aat tat ttt caa aaa caa aat aat cac tgg      204
Gly Asn Ile Arg Ser Arg Asn Tyr Phe Gln Lys Gln Asn Asn His Trp
    1               5                   10                  15
ttc cag acc agt gat tat taacccttttt tgaattatga acccctttaa            252
Phe Gln Thr Ser Asp Tyr
                20
aacctaatga aatttaagga ccctctcccc caaaatatac atataaaaaa acaaggcagt    312
ctatggacct actgagtaac tctcaagata gtaagtaagg agagaaagat ctatgtttcc    372
ctctttgata agtatgaaat atttggagga gatgctaatt tttgcacgtt tatgatattt    432
gcaatctttc atttttgtag cagattatac tcaaaaattt gatccagaac ttggccccta    492
ttctttttatc agcactttaa cttgtaaact gaaaagttta ccatcatctg tatgacatcc    552
taatgaggtt aaaaagataa aatgcagtta tgattatgat aggtataact gtatccaggt    612
ttccacagca aaaacaaaac aaaacataca ccatgttctg gggttattga cagcctcctc    672
aaaaaaaaaa aaaaa                                                     687
<210> 52
<211> 821
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<222> 46..186
<223> Von Heijne matrix
      score 9.4
      seq LILLILCVGMVVG/LV
<223> polyA_signal
<222> 781..786
<223> polyA_site
<222> 806..821
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gcaaagtcat tgaactctga gctcagttgc agtactcggg aagcc atg cag gat gaa     57
                                                 Met Gln Asp Glu
                                                     -45
gat gga tac atc acc tta aat att aaa act cgg aaa cca gct ctc gtc      105
Asp Gly Tyr Ile Thr Leu Asn Ile Lys Thr Arg Lys Pro Ala Leu Val
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            -40                 -35                 -30
tcc gtt ggc cct gca tcc tcc ttc tgg tgg cgt gtg atg gct ttg att      153
Ser Val Gly Pro Ala Ser Ser Phe Trp Trp Arg Val Met Ala Leu Ile
        -25                 -20                 -15
ctg ctg atc ctg tgc gtg ggg atg gtt gtc ggg ctg gtg gct ctg ggg      201
Leu Leu Ile Leu Cys Val Gly Met Val Val Gly Leu Val Ala Leu Gly
    -10                 -5                  1                   5
att tgg tct gtc atg cag cgc aat tac cta caa gat gag aat gaa aat      249
Ile Trp Ser Val Met Gln Arg Asn Tyr Leu Gln Asp Glu Asn Glu Asn
                10                  15                  20
cgc aca gga act ctg caa caa tta gca aag cgc ttc tgt caa tat gtg      297
Arg Thr Gly Thr Leu Gln Gln Leu Ala Lys Arg Phe Cys Gln Tyr Val
            25                  30                  35
gta aaa caa tca gaa cta aag ggc act ttc aaa ggt cat aaa tgc agc      345
Val Lys Gln Ser Glu Leu Lys Gly Thr Phe Lys Gly His Lys Cys Ser
        40                  45                  50
ccc tgt gac aca aac tgg aga tat tat gga gat agc tgc tat ggg ttc      393
Pro Cys Asp Thr Asn Trp Arg Tyr Tyr Gly Asp Ser Cys Tyr Gly Phe
    55                  60                  65
ttc agg cac aac tta aca tgg gaa gag agt aag cag tac tgc act gac      441
Phe Arg His Asn Leu Thr Trp Glu Glu Ser Lys Gln Tyr Cys Thr Asp
70                  75                  80                  85
atg aat gct act ctc ctg aag att gac aac cgg aac att gtg gag tac      489
Met Asn Ala Thr Leu Leu Lys Ile Asp Asn Arg Asn Ile Val Glu Tyr
                90                  95                  100
atc aaa gcc agg act cat tta att cgt tgg gtc gga tta tct cgc cag-     537
Ile Lys Ala Arg Thr His Leu Ile Arg Trp Val Gly Leu Ser Arg Gln
            105                 110                 115
aag tcg aat gag gtc tgg aag tgg gag gat ggc tcg gtt atc tca gaa      585
Lys Ser Asn Glu Val Trp Lys Trp Glu Asp Gly Ser Val Ile Ser Glu
        120                 125                 130
aat atg ttt gag ttt ttg gaa gat gga aaa gga aat atg aat tgt gct      633
Asn Met Phe Glu Phe Leu Glu Asp Gly Lys Gly Asn Met Asn Cys Ala
    135                 140                 145
tat ttt cat aat ggg aaa atg cac cct acc ttc tgt gag aac aaa cat      681
Tyr Phe His Asn Gly Lys Met His Pro Thr Phe Cys Glu Asn Lys His
150                 155                 160                 165
tat tta atg tgt gag agg aag gct ggc atg acc aag gtg gac caa cta      729
Tyr Leu Met Cys Glu Arg Lys Ala Gly Met Thr Lys Val Asp Gln Leu
                170                 175                 180
cct taatgcaaag aggtggacag gataacacag ataagggctt tattgtacaa           782
Pro
taaaagatat gtatgaatgc aacaaaaaaa aaaaaaaaa                          821
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<222> 81..356
<223> sig_peptide
<222> 81..152
<223> Von Heijne matrix
      score 6.2
      seq AILGSTWVALTTG/AL
<223> polyA_signal
<222> 406..411
<223> polyA_site
<222> 429..445
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ngaaaaaaaa catccgggcc gcgcggggaa ggggagacgt ggggtagagg ggagcattgc     60
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ttccttctct cgcagtgacc atg acg aaa tta gcg cag tgg ctt tgg gga cta     113
                     Met Thr Lys Leu Ala Gln Trp Leu Trp Gly Leu
                                     -20                 -15
gcg atc ctg ggc tcc acc tgg gtg gcc ctg acc acg gga gcc ttg ggc     161
Ala Ile Leu Gly Ser Thr Trp Val Ala Leu Thr Thr Gly Ala Leu Gly
            -10                 -5                  1
ctg gag ctg ccc ttg tcc tgc cag gaa gtc ctg tgg cca ctg ccc gcc     209
Leu Glu Leu Pro Leu Ser Cys Gln Glu Val Leu Trp Pro Leu Pro Ala
    5                   10                  15
tac ttg ctg gtg tcc gcc ggc tgc tat gcc ctg ggc act gtg ggc tat     257
Tyr Leu Leu Val Ser Ala Gly Cys Tyr Ala Leu Gly Thr Val Gly Tyr
20                  25                  30                  35
cgt gtg gcc act ttt cat gac tgc gag gac gcc gca cgc gag ctg cag     305
Arg Val Ala Thr Phe His Asp Cys Glu Asp Ala Ala Arg Glu Leu Gln
                40                  45                  50
agc cag ata cag gag gcc cga gcc gac tta gcc cgc agg ggg ctg cgc     353
Ser Gln Ile Gln Glu Ala Arg Ala Asp Leu Ala Arg Arg Gly Leu Arg
            55                  60                  65
ttc tgacagccta accccattcc tgtgcggaca gcccttcctc ccatttccca          406
Phe
ttaaagagcc agtttatttt ctaaaaaaaa aaaaaaaaa                          445
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<222> 72..140
<223> Von Heijne matrix
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      seq SCDCFVSVPPASA/IP
<223> polyA_signal
<222> 1482..1487
<223> polyA_site
<222> 1502..1517
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atggggcggc cctggccaga agcggaggag gtggcacccg ggaccgagct ggggtcttgg      60
aggaagagag g atg gcg tcg tcg agc cct gac tcc cca tgt tcc tgc gac     110
             Met Ala Ser Ser Ser Pro Asp Ser Pro Cys Ser Cys Asp
                        -20                 -15
tgc ttt gtc tcc gtg ccc ccg gcc tca gcc atc ccg gct gtg atc ttt     158
Cys Phe Val Ser Val Pro Pro Ala Ser Ala Ile Pro Ala Val Ile Phe
-10                 -5                  1                   5
gcc aag aac tcg gac cga ccc cgg gac gag gtg cag gag gtg gtg ttt     206
Ala Lys Asn Ser Asp Arg Pro Arg Asp Glu Val Gln Glu Val Val Phe
            10                  15                  20
gtc ccc gca ggc act cac act cct ggg agc cgg ctc cag tgc acc tac     254
Val Pro Ala Gly Thr His Thr Pro Gly Ser Arg Leu Gln Cys Thr Tyr
        25                  30                  35
att gaa gtg gaa cag gtg tcg aag acg cac gct gtg att ctg agc cgt     302
Ile Glu Val Glu Gln Val Ser Lys Thr His Ala Val Ile Leu Ser Arg
    40                  45                  50
cct tct tgg cta tgg ggg gct gag atg ggc gcc aac gag cat ggt gtc     350
Pro Ser Trp Leu Trp Gly Ala Glu Met Gly Ala Asn Glu His Gly Val
55                  60                  65                  70
tgc att ggc aac gag gct gtg tgg acg aag gag cca gtt ggg gag ggg     398
Cys Ile Gly Asn Glu Ala Val Trp Thr Lys Glu Pro Val Gly Glu Gly
                75                  80                  85
gaa gcc ctg ctg ggc atg gac cta ctc agg ctg gct ttg gaa cgg agc     446
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Glu Ala Leu Leu Gly Met Asp Leu Leu Arg Leu Ala Leu Glu Arg Ser
            90                  95                  100
agc tct gcc cag gag gcc ttg cat gtg atc aca ggg tta ctg gag cac      494
Ser Ser Ala Gln Glu Ala Leu His Val Ile Thr Gly Leu Leu Glu His
        105                 110                 115
tat ggg cag ggg ggc aac tgc ctg gag gat gct gcg cca ttc tcc tac      542
Tyr Gly Gln Gly Gly Asn Cys Leu Glu Asp Ala Ala Pro Phe Ser Tyr
    120                 125                 130
cat agc acc ttc ctg ctg gct gac cgc act gag gcg tgg gtg ctg gag      590
His Ser Thr Phe Leu Leu Ala Asp Arg Thr Glu Ala Trp Val Leu Glu
135                 140                 145                 150
aca gct ggg agg ctc tgg gct gca cag agg atc cag gag ggg gcc cgc      638
Thr Ala Gly Arg Leu Trp Ala Ala Gln Arg Ile Gln Glu Gly Ala Arg
                155                 160                 165
aac atc tcc aac cag ctg agc att ggc acg gac atc tcg gcc caa cac      686
Asn Ile Ser Asn Gln Leu Ser Ile Gly Thr Asp Ile Ser Ala Gln His
            170                 175                 180
ccg gag ctg cgg act cat gcc cag gcc aag ggc tgg tgg gat ggg cag      734
Pro Glu Leu Arg Thr His Ala Gln Ala Lys Gly Trp Trp Asp Gly Gln
        185                 190                 195
ggt gcc ttt gac ttt gct cag atc ttc tcc ctg acc cag cag cct gtg      782
Gly Ala Phe Asp Phe Ala Gln Ile Phe Ser Leu Thr Gln Gln Pro Val
    200                 205                 210
cgc atg gag gct gcc aag gcc cgc ttc cag gca ggg cgg gag ctg ctg      830
Arg Met Glu Ala Ala Lys Ala Arg Phe Gln Ala Gly Arg Glu Leu Leu
215                 220                 225                 230
cgg caa cgg caa ggg ggc atc acg gca gag gtg atg atg ggc atc ctc      878
Arg Gln Arg Gln Gly Gly Ile Thr Ala Glu Val Met Met Gly Ile Leu
                235                 240                 245
aga gac aag gag agt ggt atc tgt atg gac tcg gga ggc ttt cgc acc      926
Arg Asp Lys Glu Ser Gly Ile Cys Met Asp Ser Gly Gly Phe Arg Thr
            250                 255                 260
acg gcc agc atg gtg tct gtc ctg ccc cag gat ccc acg cag ccc tgc      974
Thr Ala Ser Met Val Ser Val Leu Pro Gln Asp Pro Thr Gln Pro Cys
        265                 270                 275
gtg cac ttt ctt acc gcc acg cca gac cca tcc agg tct gtg ttc aaa     1022
Val His Phe Leu Thr Ala Thr Pro Asp Pro Ser Arg Ser Val Phe Lys
    280                 285                 290
cct ttc atc ttc ggg gtg ggg gtg gcc cag gcc ccc cag gtg ctg tcc     1070
Pro Phe Ile Phe Gly Val Gly Val Ala Gln Ala Pro Gln Val Leu Ser
295                 300                 305                 310
ccc act ttt gga gca caa gac cct gtt cgg acc ctg ccc cga ttc cag     1118
Pro Thr Phe Gly Ala Gln Asp Pro Val Arg Thr Leu Pro Arg Phe Gln
                315                 320                 325
act cag gta gat cgt cgg cat acc ctc tac cgt gga cac cag gca gcc     1166
Thr Gln Val Asp Arg Arg His Thr Leu Tyr Arg Gly His Gln Ala Ala
            330                 335                 340
ctg ggg ctg atg gag aga gat cag gat cgg ggg cag cag ctc cag cag     1214
Leu Gly Leu Met Glu Arg Asp Gln Asp Arg Gly Gln Gln Leu Gln Gln
        345                 350                 355
aaa cag cag gat ctg gag cag gaa ggc ctc gag gcc aca cag ggg ctg     1262
Lys Gln Gln Asp Leu Glu Gln Glu Gly Leu Glu Ala Thr Gln Gly Leu
    360                 365                 370
ctg gcc ggc gag tgg gcc cca ccc ctc tgg gag ctg ggc agc ctc ttc     1310
Leu Ala Gly Glu Trp Ala Pro Pro Leu Trp Glu Leu Gly Ser Leu Phe
375                 380                 385                 390
cag gcc ttc gtg aag agg gag agc cag gct tat gcg taagcttcat          1356
Gln Ala Phe Val Lys Arg Glu Ser Gln Ala Tyr Ala
                395                 400
agcttctgct ggcctggggt ggacccagga cccctggggc ctgggtgccc tgagtggtgg   1416
taaagtggag caatcccttc acgctccttg gccatgttct gagcggccag cttggccttt   1476
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<223> sig_peptide
<222> 194..379
<223> Von Heijne matrix
      score 4.6
      seq HILTVPLLEPARC/SG
<223> polyA_site
<222> 1545..1560
<400> 55
cattcataaa tattctctta ccatttttact tgacaattat tttaggctta cagaaaagtg      60
gccagagtag tgcagggctc ctatagttgg cttcccctgt tgccatcatc tcgtctgatc     120
gtagggcagg ttagcattgc tacaggcctc ttacccggcc tacagctctt aggcacatct     180
gtccatttga cta atg gcc att ttc tgg ata gtc cat gct cac ttc tgg         229
              Met Ala Ile Phe Trp Ile Val His Ala His Phe Trp
                        -60                 -55
agc ccc ctc cca ccc agg ctc cca cat ggc cgg tgc tgt tgc ctg aag       277
Ser Pro Leu Pro Pro Arg Leu Pro His Gly Arg Cys Cys Cys Leu Lys
-50                 -45                 -40                 -35
gcc cct ctt cct cct gac gtg gga ccc ctt cag gta gcc ccg cat ctt       325
Ala Pro Leu Pro Pro Asp Val Gly Pro Leu Gln Val Ala Pro His Leu
                -30                 -25                 -20
ttc agc gtg ccc ctt cac att ctg act gtt cct ctt ctg gaa cct gca       373
Phe Ser Val Pro Leu His Ile Leu Thr Val Pro Leu Leu Glu Pro Ala
            -15                 -10                 -5
aga tgc tct ggg atc ctt gta ttt ttc ctg cac cag ccc gtt tca tcc       421
Arg Cys Ser Gly Ile Leu Val Phe Phe Leu His Gln Pro Val Ser Ser
        1               5                   10
ctg agc ttc tgt tat ttt att gga gga tgg tgc tagaaacaca ggtctggatg     474
Leu Ser Phe Cys Tyr Phe Ile Gly Gly Trp Cys
15                  20                  25
caggcaggag acacacgcgt ccacactagc atgcgtgtgt acacacatct acatgtgctt     534
atccccccgcg ttcatgttaa aaaccatggg atcataccgg tgtttcagat tcacatccac     594
cccagcaggg tttctcgccc ccattgctta taaccttagc aggtgttgag aaccctggcg     654
ctcactgtcc acagtgagtt tgcttattcg ttgaaaccta gcgtgcctgt agagtgtgga     714
gagttgccgg cccgcacccc tgcgagacac agactttctg accgcagccc tcatgtgtgt     774
ggctcttctt gtccttggcc ttacagtgca gtcggatcgc tgctttccag agttgcctgg     834
gggtaggtcc ctcctcttct gtgctctgcg gcgcagtgag cggcctttgc ctcaggcctc     894
ccgcggcttc cttaagcctc tggcctgccc ggtccctggc gccaggtctg ttttccctgc     954
tcccttctct ctgatcctgc tttggtctga gccgtgcctc tgggccccag cattgctggg    1014
ccgcattgtc gttttatttc tcttgtgtcg ttgcgtctag tgtaagacat tcagtggatc    1074
attgtggatg gtcattagtg gtccagagtg gaaagtgagg tcgttgttgg tggtgtacct    1134
acagtgcctg ttagggagct gttcctggtg ttgcccgtga atattagact tgctcccgag    1194
cctgcgccac agcccatccc tagcgactta gcgacagtgg ctgccaggtg cgggtggctg    1254
tgtcttgtat acactgtgtg ggcagcccag ggccaggggc ctcctccttc catggcagcc    1314
tctgtctgca tcacagagat aaggccgcgg ctgccaccag gataaggagc cagcagctgc    1374
tctcggagga gccgccctga cccctcccca tcatgccgcc gtggggtttc catgcagaat    1434
tttccttggg cagagttgct ttttgattct agtttttaaa aaaactgttc tttccatcat    1494
gataaaaaga aagacatgct catttcaaat agtttaggag atgtggaagc aaaaaaaaaa    1554
aaaaaa                                                               1560
<210> 56
<211> 1066
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<213> Homo sapiens
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<223> sig_peptide
<222> 48..347
<223> Von Heijne matrix
score 3.7
seq LASSFLFTMGGLG/FI
<223> polyA_signal
<222> 1031..1036
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<222> 1051..1066
<400> 56

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                                                    Met Glu Thr
                                                    -100
ttg tac cgt gtc ccg ttc tta gtg ctc gaa tgt ccc aac ctg aag ctg      104
Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn Leu Lys Leu
        -95                 -90                 -85
aag aag ccg ccc tgg ttg cac atg ccg tcg gcc atg act gtg tat gct      152
Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr Val Tyr Ala
    -80                 -75                 -70
ctg gtg gtg gtg tct tac ttc ctc atc acc gga gga ata att tat gat      200
Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile Ile Tyr Asp
-65                 -60                 -55                 -50
gtt att gtt gaa cct cca agt gtc ggt tct atg act gat gaa cat ggg      248
Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp Glu His Gly
                -45                 -40                 -35
cat cag agg cca gta gct ttc ttg gcc tac aga gta aat gga caa tat      296
His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn Gly Gln Tyr
            -30                 -25                 -20
att atg gaa gga ctt gca tcc agc ttc cta ttt aca atg gga ggt tta      344
Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met Gly Gly Leu
        -15                 -10                 -5
ggt ttc ata atc ctg gac cga tcg aat gca cca aat atc cca aaa ctc      392
Gly Phe Ile Ile Leu Asp Arg Ser Asn Ala Pro Asn Ile Pro Lys Leu
    1                   5                   10                  15
aat aga ttc ctt ctt ctg ttc att gga ttc gtc tgt gtc cta ttg agt      440
Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val Leu Leu Ser
                20                  25                  30
ttt ttc atg gct aga gta ttc atg aga atg aaa ctg ccg ggc tat ctg      488
Phe Phe Met Ala Arg Val Phe Met Arg Met Lys Leu Pro Gly Tyr Leu
            35                  40                  45
atg ggt tagagtgcct ttgagaagaa atcagtggat actggatttg ctcctgtcaa       544
Met Gly
tgaagtttta aaggctgtac caatcctcta atatgaaatg tggaaaagaa tgaagagcag    604
cagtaaaaga aatatctagt gaaaaaacag gaagcgtatt gaagcttgga ctagaatttc    664
ttcttggtat taaagagaca agtttatcac agaatttttt ttcctgctgg cctattgcta    724
taccaatgat gttgagtggc attttctttt tagtttttca ttaaaatata ttccatatct    784
acaactataa tatcaaataa agtgattatt ttttacaacc ctcttaacat tttttggaga    844
tgacatttct gattttcaga aattaacata aaatccagaa gcaagattcc gtaagctgag    904
aactctggac agttgatcag ctttacctat ggtgctttgc ctttaactag agtgtgtgat    964
ggtagattat ttcagatatg tatgtaaaac tgtttcctga acaataagat gtatgaacgg   1024
agcagaaata aatacttttt ctaattaaaa aaaaaaaaaa aa                      1066
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<222> 111..671
<223> sig_peptide
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<223> Von Heijne matrix
      score 4.5
      seq SFTVSMAIGLVLG/GF
<223> polyA_signal
<222> 990..995
<223> polyA_site
<222> 1045..1061
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tggtttttct ttctgttttt cttctctttc ttctatttct tgtggatatt atg gct         116
                                                        Met Ala
                                                        -35
aat aac aca aca agt tta ggg agt cca tgg cca gaa aac ttt tgg gag         164
Asn Asn Thr Thr Ser Leu Gly Ser Pro Trp Pro Glu Asn Phe Trp Glu
            -30                 -25                 -20
gac ctt atc atg tcc ttc act gta tcc atg gca atc ggg ctg gta ctt         212
Asp Leu Ile Met Ser Phe Thr Val Ser Met Ala Ile Gly Leu Val Leu
        -15                 -10                 -5
gga gga ttt att tgg gct gtg ttc att tgt ctg tct cga aga aga aga         260
Gly Gly Phe Ile Trp Ala Val Phe Ile Cys Leu Ser Arg Arg Arg Arg
    1               5                   10                  15
gcc agt gct ccc atc tca cag tgg agt tca agc agg aga tct agg tct         308
Ala Ser Ala Pro Ile Ser Gln Trp Ser Ser Ser Arg Arg Ser Arg Ser
                20                  25                  30
tct tac acc cac ggc ctc aac aga act gga ttt tac cgc cac agt ggc         356
Ser Tyr Thr His Gly Leu Asn Arg Thr Gly Phe Tyr Arg His Ser Gly
            35                  40                  45
tgt gaa cgt cga agc aac ctc agc ctg gcc agt ctc acc ttc cag cga         404
Cys Glu Arg Arg Ser Asn Leu Ser Leu Ala Ser Leu Thr Phe Gln Arg
        50                  55                  60
caa gct tcc ctg gaa caa gca aat tcc ttt cca aga aaa tca agt ttc         452
Gln Ala Ser Leu Glu Gln Ala Asn Ser Phe Pro Arg Lys Ser Ser Phe
    65                  70                  75
aga gct tct act ttc cat ccc ttt ctg caa tgt cca cca ctt cct gtg         500
Arg Ala Ser Thr Phe His Pro Phe Leu Gln Cys Pro Pro Leu Pro Val
80                  85                  90                  95
gaa act gag agt cag ctg gtg act ctc cct tct tcc aat atc tct ccc         548
Glu Thr Glu Ser Gln Leu Val Thr Leu Pro Ser Ser Asn Ile Ser Pro
                100                 105                 110
acc atc agc act tcc cac agt ctg agc cgt cct gac tac tgg tcc agt         596
Thr Ile Ser Thr Ser His Ser Leu Ser Arg Pro Asp Tyr Trp Ser Ser
            115                 120                 125
aac agt ctt cga gtg ggc ctt tca aca ccg ccc cca cct gcc tat gag         644
Asn Ser Leu Arg Val Gly Leu Ser Thr Pro Pro Pro Pro Ala Tyr Glu
        130                 135                 140
tcc atc atc aag gca ttc cca gat tcc tgagtagggt ggcttttggt               691
Ser Ile Ile Lys Ala Phe Pro Asp Ser
    145                 150
ttttgtttct ttcttgtctt gtcttttatt gaaaggaaat caaaaatagg ctaaacagaa      751
ttttgagggc atggcccaaa taactcatga gttccaagtt gaaacatggt tgtgcaagtt      811
ggacattaca atgtaaaaca cattttcttc aaacacgttt tccctttttgt ttcaaaaaat     871
gtaatatttt cccccaagcg ttttatattt atgtattttg tattcaatgt gaggcttatt      931
aaaaatagtg attctaatgt aagaatcagc taagatgcat tatatatatt ttaattaaaa      991
ttaaaacttc agatatttgt ggattacaat cctcatttac ttccaatgtg actaaaaaaa     1051
aaaaaaaaaa                                                           1061
<210> 58
<211> 2025
<212> DNA
<213> Homo sapiens
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<223> CDS
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<223> sig_peptide
<222> 5..82
<223> Von Heijne matrix
score 4
seq SLFWFTVITLSFG/YY
<223> polyA_signal
<222> 1986..1991
<223> polyA_site
<222> 2010..2025
<400> 58

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     Met Ala Thr Ala Ala Gly Ala Thr Tyr Phe Gln Arg Gly Ser Leu
        -25                 -20                 -15
ttc tgg ttc aca gtc atc acc ctc agc ttt ggc tac tac aca tgg gtt      97
Phe Trp Phe Thr Val Ile Thr Leu Ser Phe Gly Tyr Tyr Thr Trp Val
    -10                 -5                  1               5
gtc ttc tgg cct cag agt atc cct tat cag aac ctt ggg ccc ctg ggc     145
Val Phe Trp Pro Gln Ser Ile Pro Tyr Gln Asn Leu Gly Pro Leu Gly
                10                  15                  20
ccc ttc act cag tac ttg gtg gac cac cat cac acc ctc ctg tgc aat     193
Pro Phe Thr Gln Tyr Leu Val Asp His His His Thr Leu Leu Cys Asn
            25                  30                  35
ggg tat tgg ctt gcc tgg ctg att cat gtg gga gag tcc ttg tat gcc     241
Gly Tyr Trp Leu Ala Trp Leu Ile His Val Gly Glu Ser Leu Tyr Ala
        40                  45                  50
ata gta ttg tgc aag cat aaa ggc atc aca agt ggt cgg gct cag cta     289
Ile Val Leu Cys Lys His Lys Gly Ile Thr Ser Gly Arg Ala Gln Leu
    55                  60                  65
ctc tgg ttc cta cag act ttc ttc ttt ggg ata gcg tct ctc acc atc     337
Leu Trp Phe Leu Gln Thr Phe Phe Phe Gly Ile Ala Ser Leu Thr Ile
70                  75                  80                  85
ttg att gct tac aaa cgg aag cgc caa aaa caa act tgaagttgtc          383
Leu Ile Ala Tyr Lys Arg Lys Arg Gln Lys Gln Thr
                90                  95
tgaaagcttg ctctacactt ttacattcat cctcaccctt ttttttgtgg ggtagaggag   443
gtgcagtaat ttactcagtg atctttctac tttctagaaa ctgtccttca aagctcttta   503
agacccccctc gttagtcagt tttttctctt atatgctctg gttgagcttg aatagaccag   563
ttgttactta agaaagaaac agagaaagat tttagctttt caatcctatt tggcagagga   623
cttcagctac cttcttacag tctttggctg tgttggtacc ctcgtgtgct ctgagctaag   683
ccacatacta aactgacttt ttggtttgta tacccttgct cccgccttct gatgaaaaca   743
ccttaccctc acaaccacca tctttcctct cctttccaaa gctctttcca ccttgctgca   803
ctaagataaa gtgacacttc cactatatgt caattccaca cacatttatt aggtacctgt   863
gaggtaggat cctatcctct caaacttcca tttctcatgc tacagagaaa gataaggaag   923
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gaacctggag gggagactgc agagtgcctt ccctgatgct gcagccggaa gtgatccttc  1043
cctccacctg gcccctggga cactgtgctc tgcagtgtgc agggcctgat ggcactgcta  1103
gattgctcct tcagctcagg gccacagctt aaacagcttt acctttcccc tcagcacctg  1163
tcccactatc ttgcacacag gtgctctaac catgtttatt gaacaaagga gggaaactga  1223
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accagatttc ttaatacctg gtcttcctca aagagaaata ataacagtaa tagtggtgct   1943
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                       -100                -95
ctt ttg gcg gca gcg gcg acg cga ggg ctc ccg gcc gcc cgc gtc cgc        97
Leu Leu Ala Ala Ala Ala Thr Arg Gly Leu Pro Ala Ala Arg Val Arg
-90                 -85                 -80                 -75
tgg gaa tct agc ttc tcc agg act gtg gtc gcc ccg tcc gct gtg gcg       145
Trp Glu Ser Ser Phe Ser Arg Thr Val Val Ala Pro Ser Ala Val Ala
                -70                 -65                 -60
gga aag cgg ccc cca gaa ccg acc aca ccg tgg caa gag gac cca gaa       193
Gly Lys Arg Pro Pro Glu Pro Thr Thr Pro Trp Gln Glu Asp Pro Glu
            -55                 -50                 -45
ccc gag gac gaa aac ttg tat gag aag aac cca gac tcc cat ggt tat       241
Pro Glu Asp Glu Asn Leu Tyr Glu Lys Asn Pro Asp Ser His Gly Tyr
        -40                 -35                 -30
gac aag gac ccc gtt ttg gac gtc tgg aac atg cga ctt gtc ttc ttc       289
Asp Lys Asp Pro Val Leu Asp Val Trp Asn Met Arg Leu Val Phe Phe
    -25                 -20                 -15
ttt ggc gtc tcc atc atc ctg gtc ctt ggc agc acc ttt gtg gcc tat       337
Phe Gly Val Ser Ile Ile Leu Val Leu Gly Ser Thr Phe Val Ala Tyr
-10                 -5                  1                   5
ctg cct gac tac agg atg aaa gag tgg tcc cgc cgc gaa gct gag agg       385
Leu Pro Asp Tyr Arg Met Lys Glu Trp Ser Arg Arg Glu Ala Glu Arg
            10                  15                  20
ctt gtg aaa tac cga gag gcc aat ggc ctt ccc atc atg gaa tcc aac       433
Leu Val Lys Tyr Arg Glu Ala Asn Gly Leu Pro Ile Met Glu Ser Asn
        25                  30                  35
tgc ttc gac ccc agc aag atc cag ctg cca gag gat gag tgaccagttg       482
Cys Phe Asp Pro Ser Lys Ile Gln Leu Pro Glu Asp Glu
    40                  45                  50
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gtt gat tta tgg ata gtt tgt att ttc act gta tct gtc tca cac ctt 97
Val Asp Leu Trp Ile Val Cys Ile Phe Thr Val Ser Val Ser His Leu
20 25 30
ttt gaa aag gga aca ttg tat ggc tac ttt tat gtg att aac tcc tcc 145
Phe Glu Lys Gly Thr Leu Tyr Gly Tyr Phe Tyr Val Ile Asn Ser Ser
35 40 45
atc aat tta tgt gtc aat gat tgc ctt cct gta atg gat tca att tct 193
Ile Asn Leu Cys Val Asn Asp Cys Leu Pro Val Met Asp Ser Ile Ser
50 55 60
ctg tct cca ttg ttt ctt tct cac tagagaagtt ctttaaaatt ctatgaaaat 247
Leu Ser Pro Leu Phe Leu Ser His
65 70
gaaactgtgc taaattaaaa atctactcat gataacagga gacactcaaa attatgggtt 307
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aaataaacct ttgccatcag ttcaccaaaa gcactcatga gaggaaaaat ggcatatcac 427
taaatataga gttctttgtc acttcttgat ttcaaattta caactaatac tcaacacttt 487
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Met Glu
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Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser Tyr Thr
-15 -10 -5
ctg gcc aga gat acc aca gtc aaa cct gga gcc aaa aag gac aca aag 152
Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp Thr Lys
1 5 10
gac tct cga ccc aaa ctg ccc cag acc ctc tcc aga ggt tgg ggt gac 200
Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp Gly Asp
15 20 25 30
caa ctc atc tgg act cag aca tat gaa gaa gct cta tat aaa tcc aag 248
Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys Ser Lys
35 40 45
aca agc aac aaa ccc ttg atg att att cat cac ttg gat gag tgc cca 296
Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu Cys Pro
50 55 60
cac agt caa gct tta aag aaa gtg ttt gct gaa aat aaa gaa atc cag 344
His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu Ile Gln
65 70 75

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aaa ttg gca gag cag ttt gtc ctc ctc aat ctg gtt tat gaa aca act      392
Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu Thr Thr
    80                  85                  90
gac aaa cac ctt tct cct gat ggc cag tat gtc ccc agg att atg ttt      440
Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val Pro Arg Ile Met Phe
95                  100                 105                 110
gtt gac cca tct ctg aca gtt aga gcc gat atc act gga aga tat tca      488
Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg Tyr Ser
                115                 120                 125
aat cgt ctc tat gct tac gaa cct gca gat aca gct ctg ttg ctt gac      536
Asn Arg Leu Tyr Ala Tyr Glu Pro Ala Asp Thr Ala Leu Leu Leu Asp
            130                 135                 140
aac atg aag aaa gct ctc aag ttg ctg aag act gaa ttg taaagaaaaa       585
Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr Glu Leu
        145                 150                 155
aaatctccaa gcccttctgt ctgtcaggcc ttgagacttg aaaccagaag aagtgtgaga    645
agactggcta gtgtggaagc atagtgaaca cactgattag gttatggttt aatgttacaa    705
caactatttt ttaagaaaaa caagttttag aaatttggtt tcaagtgtac atgtgtgaaa    765
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gtgccatc atg gcg gac gcg gcc agt cag gtg ctc ctg ggc tcc ggt ctc     110
        Met Ala Asp Ala Ala Ser Gln Val Leu Leu Gly Ser Gly Leu
        -20                 -15                 -10
acc atc ctg tcc cag ccg ctc atg tac gtg aaa gtg ctc atc cag gtg      158
Thr Ile Leu Ser Gln Pro Leu Met Tyr Val Lys Val Leu Ile Gln Val
    -5                  1                   5                   10
gga tat gag cct ctt cct cca aca ata gga cga aat att ttt ggg cgg      206
Gly Tyr Glu Pro Leu Pro Pro Thr Ile Gly Arg Asn Ile Phe Gly Arg
                15                  20                  25
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caa gtg tgt cag ctt cct ggt ctc ttt agt tat gct cag cac att gcc      254
Gln Val Cys Gln Leu Pro Gly Leu Phe Ser Tyr Ala Gln His Ile Ala
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agt atc gat ggg agg cgc ggg ttg ttc aca ggc tta act cca aga ctg      302
Ser Ile Asp Gly Arg Arg Gly Leu Phe Thr Gly Leu Thr Pro Arg Leu
      45                  50                  55
tgt tcg gga gtc ctt gga act gtg gtc cat ggt aaa gtt tta cag cat      350
Cys Ser Gly Val Leu Gly Thr Val Val His Gly Lys Val Leu Gln His
  60                  65                  70
tac cag gag agt gac aag ggt gag gag tta gga cct gga aat gta cag      398
Tyr Gln Glu Ser Asp Lys Gly Glu Glu Leu Gly Pro Gly Asn Val Gln
75                  80                  85                  90
aaa gaa gtc tca tct tcc ttt gac cac gtt atc aag gag aca act cga      446
Lys Glu Val Ser Ser Ser Phe Asp His Val Ile Lys Glu Thr Thr Arg
              95                  100                 105
gag atg atc gct cgt tct gct gct acc ctc atc aca cat ccc ttc cat      494
Glu Met Ile Ala Arg Ser Ala Ala Thr Leu Ile Thr His Pro Phe His
          110                 115                 120
gtg atc act ctg aga tct atg gta cag ttc att ggc aga gaa tcc aag      542
Val Ile Thr Leu Arg Ser Met Val Gln Phe Ile Gly Arg Glu Ser Lys
      125                 130                 135
tac tgt gga ctt tgt gat tcc ata ata acc atc tat cgg gaa gag ggc      590
Tyr Cys Gly Leu Cys Asp Ser Ile Ile Thr Ile Tyr Arg Glu Glu Gly
  140                 145                 150
att cta gga ttt ttc gcg ggt ctt gtt cct cgc ctt cta ggt gac atc      638
Ile Leu Gly Phe Phe Ala Gly Leu Val Pro Arg Leu Leu Gly Asp Ile
155                 160                 165                 170
ctt tct ttg tgg ctg tgt aac tca ctg gcc tac ctc gtc aat acc tat      686
Leu Ser Leu Trp Leu Cys Asn Ser Leu Ala Tyr Leu Val Asn Thr Tyr
              175                 180                 185
gca ctg gac agt ggg gtt tct acc atg aat gaa atg aag agt tat tct      734
Ala Leu Asp Ser Gly Val Ser Thr Met Asn Glu Met Lys Ser Tyr Ser
          190                 195                 200
caa gct gtc aca gga ttt ttt gcg agt atg ttg acc tat ccc ttt gtg      782
Gln Ala Val Thr Gly Phe Phe Ala Ser Met Leu Thr Tyr Pro Phe Val
      205                 210                 215
ctt gtc tcc aat ctt atg gct gtc aac aac tgt ggt ctt gct ggt gga      830
Leu Val Ser Asn Leu Met Ala Val Asn Asn Cys Gly Leu Ala Gly Gly
  220                 225                 230
tgc cct cct tac tcc cca ata tat acg tct tgg ata gac tgt tgg tgc      878
Cys Pro Pro Tyr Ser Pro Ile Tyr Thr Ser Trp Ile Asp Cys Trp Cys
235                 240                 245                 250
atg cta caa aaa gag ggg aat atg agc cga gga aat agc tta ttt ttc      926
Met Leu Gln Lys Glu Gly Asn Met Ser Arg Gly Asn Ser Leu Phe Phe
              255                 260                 265
cgg aag gtc ccc ttt ggg aag act tat tgt tgt gac ctg aaa atg tta      974
Arg Lys Val Pro Phe Gly Lys Thr Tyr Cys Cys Asp Leu Lys Met Leu
          270                 275                 280
att tgaagatgtg gggcagggac agtgacattt ctgtagtccc agatgcacag          1027
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Met Ser Thr Gly
att atg gag tac aaa aaa act aca aaa gca atg aaa aaa aag aag gat 103
Ile Met Glu Tyr Lys Lys Thr Thr Lys Ala Met Lys Lys Lys Lys Asp
-35 -30 -25 -20
gtt tta ttt aca tcc tat ttc aaa acc att gct ttc ttg cta ttg tat 151
Val Leu Phe Thr Ser Tyr Phe Lys Thr Ile Ala Phe Leu Leu Leu Tyr
-15 -10 -5
gtc tct gca ggc cca ata tcg cga atc ttc ata aga agt tta gaa ttg 199
Val Ser Ala Gly Pro Ile Ser Arg Ile Phe Ile Arg Ser Leu Glu Leu
1 5 10
ttc ctt atg ttt cct tct aac aaa cac tgg tat att tca tgaaagtgta 248
Phe Leu Met Phe Pro Ser Asn Lys His Trp Tyr Ile Ser
15 20 25
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acaacggctg tgtgtttttc catacagata ttctaatttt tttattatgc agctaatttt 428
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Met
ggg ttc gga gcg acc ttg gcc gtt ggc ctg acc atc ttt gtg ctg tct 164
Gly Phe Gly Ala Thr Leu Ala Val Gly Leu Thr Ile Phe Val Leu Ser
-15 -10 -5
gtc gtc act atc atc atc tgc ttc acc tgc tcc tgc tgc tgc ctt tac 212
Val Val Thr Ile Ile Ile Cys Phe Thr Cys Ser Cys Cys Cys Leu Tyr
1 5 10 15
aag acg tgc cgc cga cca cgt ccg gtt gtc acc acc acc aca tcc acc 260
Lys Thr Cys Arg Arg Pro Arg Pro Val Val Thr Thr Thr Thr Ser Thr
20 25 30
act gtg gtg cat gcc cct tat cct cag cct cca agt gtg ccg ccc agc 308
Thr Val Val His Ala Pro Tyr Pro Gln Pro Pro Ser Val Pro Pro Ser
35 40 45
tac cct gga cca agc tac cag ggc tac cac acc atg ccg cct cag cca 356

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Gly Met Pro Ala Ala Pro Tyr Pro Met Gln Tyr Pro Pro Pro Tyr Pro
65                  70                  75                  80
gcc cag ccc atg ggc cca ccg gcc tac cac gag acc ctg gct gga gga      452
Ala Gln Pro Met Gly Pro Pro Ala Tyr His Glu Thr Leu Ala Gly Gly
                85                  90                  95
gca gcc gcg ccc tac ccc gcc agc cag cct cct tac aac ccg gcc tac      500
Ala Ala Ala Pro Tyr Pro Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr
            100                 105                 110
atg gat gcc ccg aag gcg gcc ctc tgagcattcc ctggcctctc tggctgccac     554
Met Asp Ala Pro Lys Ala Ala Leu
        115                 120
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                                      -10                 -5
gta ctg ctg ggc ggc ttc ttc gcg ctc gtg ggg ttg gcc aag ctc tcg      100
Val Leu Leu Gly Gly Phe Phe Ala Leu Val Gly Leu Ala Lys Leu Ser
                1               5                   10
gag gag atc tcg gct cca gtt tcg gag cgg atg aat gcc ctg ttc gtg      148
Glu Glu Ile Ser Ala Pro Val Ser Glu Arg Met Asn Ala Leu Phe Val
        15                  20                  25
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cag ttt gct gag gtg ttc ccg ctg aag gta ttt ggc tac cag cca gat      196
Gln Phe Ala Glu Val Phe Pro Leu Lys Val Phe Gly Tyr Gln Pro Asp
    30                  35                  40
ccc ctg aac tac caa ata gct gtg ggc ttt ctg gaa ctg ctg gct ggg      244
Pro Leu Asn Tyr Gln Ile Ala Val Gly Phe Leu Glu Leu Leu Ala Gly
45                  50                  55                  60
ttg ctg ctg gtc atg ggc cca ccg atg ctg caa gag atc agt aac ttg      292
Leu Leu Leu Val Met Gly Pro Pro Met Leu Gln Glu Ile Ser Asn Leu
                65                  70                  75
ttc ttg att ctg ctc atg atg ggg gct atc ttc acc ttg gca gct ctg      340
Phe Leu Ile Leu Leu Met Met Gly Ala Ile Phe Thr Leu Ala Ala Leu
            80                  85                  90
aaa gag tca cta agc acc tgt atc cca gcc att gtc tgc ctg ggg ttc      388
Lys Glu Ser Leu Ser Thr Cys Ile Pro Ala Ile Val Cys Leu Gly Phe
        95                  100                 105
ctg ctg ctg ctg aat gtc ggc cag ctc tta gcc cag act aag aag gtg      436
Leu Leu Leu Leu Asn Val Gly Gln Leu Leu Ala Gln Thr Lys Lys Val
    110                 115                 120
gtc aga ccc act agg aag aag act cta agt aca ttc aag gaa tcc tgg      484
Val Arg Pro Thr Arg Lys Lys Thr Leu Ser Thr Phe Lys Glu Ser Trp
125                 130                 135                 140
aag tagagcatct ctgtctcttt atgccatgca gctgtcacag caggaacatg           537
Lys
gtagaacaca gagtctatca tcttgttacc agtataatat ccagggtcag ccagtgttga    597
aagagacatt ttgtctacct ggcactgctt tctcttttta gctttactac tcttttgtga    657
ggagtacatg ttatgcatat taacattcct catatcatat gaaaatacaa aataagcaga    717
aaagaaattt aaatcaacca aaattctgat gccccaaata accactttta atgccttggt    777
gtaagtatac ctctgaactt ttttctgtgc ctttaaacag atatatattt ttttaaatg     837
aaaataaaac catatatcct attttatttc ctccttttaa aaccttataa actataacac    897
tgcaaaaaaa aaaaaaaaaa                                               917
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      score 3.6
      seq RALSTFLFGSIRG/AA
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<223> polyA_site
<222> 627..641
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gccagtgcgc agacgcaggg gtcggcgccg ggtgagagcg tgcggccggg taagggcgtg     60
tggccggatt caccacaac atg gca aat ctt ttt ata agg aaa atg gtg aac     112
                  Met Ala Asn Leu Phe Ile Arg Lys Met Val Asn
                  -35                 -30
cct ctg ctc tat ctc agt cgt cac acg gtg aag cct cga gcc ctc tcc      160
Pro Leu Leu Tyr Leu Ser Arg His Thr Val Lys Pro Arg Ala Leu Ser
-25                 -20                 -15                 -10
aca ttt cta ttt gga tcc att cga ggt gca gcc ccc gtg gct gtg gaa      208
Thr Phe Leu Phe Gly Ser Ile Arg Gly Ala Ala Pro Val Ala Val Glu
                -5                  1                   5
ccc ggg gca gca gtg cgc tca ctt ctc tca ccc ggc ctc ctg ccc cat      256
Pro Gly Ala Ala Val Arg Ser Leu Leu Ser Pro Gly Leu Leu Pro His
        10                  15                  20
ctg ctg cct gcg ctg ggg ttc aaa aac aag act gtc ctt aat aag cgc      304
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Leu Leu Pro Ala Leu Gly Phe Lys Asn Lys Thr Val Leu Asn Lys Arg
    25                  30                  35
tgc aag gac tgt tac ctg gtg aag agg cgg ggt cgg tgg tac gtc tac      352
Cys Lys Asp Cys Tyr Leu Val Lys Arg Arg Gly Arg Trp Tyr Val Tyr
40                  45                  50                  55
tgt aaa acc cat ccg agg cac aag cag aga cag atg tagacccttt          398
Cys Lys Thr His Pro Arg His Lys Gln Arg Gln Met
                60                  65
ccctccagac tcacgcacat actcgtcatc gcatcacttg ggagaatggt tgtatcttat   458
ggaaggaatt atcacatcaa ggagtcaggg gaaagtgact ggaagcaaac gccctaaaag   518
ttacccatca cgtttcagtg taaatgagta actatagaag acattgcgtt atcttatttc   578
caaaacgttc caactaaaaa acattttcct attaaaatag accttccgaa aaaaaaaaaa   638
aaa                                                                641
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      seq ISCTCLLLYLTHC/IL
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gcctggactc attttcactc ccatcttcag tcatccccta actcccccac agtcagtccc   180
caaag atg cca tat gct ttc act tct cca tgc cct tgc tca ttt gtc tca    230
      Met Pro Tyr Ala Phe Thr Ser Pro Cys Pro Cys Ser Phe Val Ser
                    -70                 -65                 -60
ttg cct gaa ata tcc ttt tat ttc acc aaa ctg ctg ctc atc ctc aag     278
Leu Pro Glu Ile Ser Phe Tyr Phe Thr Lys Leu Leu Leu Ile Leu Lys
                -55                 -50                 -45
gcc ctg cct gag tca cct ttc ctt ctt gct tcc tcc ccc ttg cct cct     326
Ala Leu Pro Glu Ser Pro Phe Leu Leu Ala Ser Ser Pro Leu Pro Pro
            -40                 -35                 -30
ctc ccc act acc cta aga aaa ttc atc cct ccc cct tca tta ata tca     374
Leu Pro Thr Thr Leu Arg Lys Phe Ile Pro Pro Pro Ser Leu Ile Ser
        -25                 -20                 -15
tgc aca tgc ttg tta tta tat tta aca cat tgt ata tta ggt att tgt     422
Cys Thr Cys Leu Leu Leu Tyr Leu Thr His Cys Ile Leu Gly Ile Cys
    -10                 -5                  1                   5
ttt gct tat cct ttt atc cta tgaaattgtg aacaatttgt tgaataattg        473
Phe Ala Tyr Pro Phe Ile Leu
                10
aataatcaca tatcaaaatg tagagaggtt atttgtctct tccctgtagg actccatttt   533
caggcagtgt ctgctaagaa tccccttgac ctgggattgg aagttgtttc tcccactgct   593
gagctccttt atattagctc ttcacctctc actcctttgt ttcttctctt ggcactttac   653
gtctttctac ccatttaatt tgataaatgt ctcatgtcat ctttaaaact gaaggtgaca   713
catgtctggt ttatctttat aactcaaaaa tgttgagctt aatgcagaat ggagaatagc   773
tacttagtaa atttttaaaa tacatgctac cattttaag gggagaagaa gacaatatac    833
atgacaaaaa aaaaaaaaaa a                                             854
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score 4.4
seq VLILLFSLALIIL/PS
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<222> 1536..1541
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<222> 1553..1568
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ttcagaacag aagc atg gat ctc gga atc cct gac ctg ctg gac gcg tgg      110
                Met Asp Leu Gly Ile Pro Asp Leu Leu Asp Ala Trp
                -310                -305                -300
ctg gag ccc cca gag gat atc ttc tcg aca gga tcc gtc ctg gag ctg      158
Leu Glu Pro Pro Glu Asp Ile Phe Ser Thr Gly Ser Val Leu Glu Leu
            -295                -290                -285
gga ctc cac tgc ccc cct cca gag gtt ccg gta act agg cta cag gaa      206
Gly Leu His Cys Pro Pro Pro Glu Val Pro Val Thr Arg Leu Gln Glu
        -280                -275                -270
cag gga ctg caa ggc tgg aag tcc ggt ggg gac cgt ggc tgt ggc ctt      254
Gln Gly Leu Gln Gly Trp Lys Ser Gly Gly Asp Arg Gly Cys Gly Leu
    -265                -260                -255
caa gag agt gag cct gaa gat ttc ttg aag ctt ttc att gat ccc aat      302
Gln Glu Ser Glu Pro Glu Asp Phe Leu Lys Leu Phe Ile Asp Pro Asn
-250                -245                -240                -235
gag gtg tac tgc tca gaa gca tct cct ggc agt gac agt ggc atc tct      350
Glu Val Tyr Cys Ser Glu Ala Ser Pro Gly Ser Asp Ser Gly Ile Ser
                -230                -225                -220
gag gac tcc tgc cat cca gac agt ccc cct gcc ccc agg gca acc agt      398
Glu Asp Ser Cys His Pro Asp Ser Pro Pro Ala Pro Arg Ala Thr Ser
            -215                -210                -205
tct cct atg ctc tat gag gtt gtc tat gag gca ggg gcc ctg gag agg      446
Ser Pro Met Leu Tyr Glu Val Val Tyr Glu Ala Gly Ala Leu Glu Arg
        -200                -195                -190
atg cag ggg gaa act ggg cca aat gta ggc ctt atc tcc atc cag cta      494
Met Gln Gly Glu Thr Gly Pro Asn Val Gly Leu Ile Ser Ile Gln Leu
    -185                -180                -175
gat cag tgg agc cca gca ttt atg gtg cct gat tcc tgc atg gtc agt      542
Asp Gln Trp Ser Pro Ala Phe Met Val Pro Asp Ser Cys Met Val Ser
-170                -165                -160                -155
gag ctg ccc ttt gat gct cat gcc cac atc ctg ccc aga gca ggc acc      590
Glu Leu Pro Phe Asp Ala His Ala His Ile Leu Pro Arg Ala Gly Thr
                -150                -145                -140
gta gcc cca gtg ccc tgt aca acc ctg ctg ccc tgt caa acc ctg ttc      638
Val Ala Pro Val Pro Cys Thr Thr Leu Leu Pro Cys Gln Thr Leu Phe
            -135                -130                -125
ctg acc gat gag gag aag cgt ctg ctg ggg cag gaa ggg gtt tcc ctg      686
Leu Thr Asp Glu Glu Lys Arg Leu Leu Gly Gln Glu Gly Val Ser Leu
        -120                -115                -110
ccc tct cac ctg ccc ctc acc aag gca gag gag agg gtc ctc aag aag      734
Pro Ser His Leu Pro Leu Thr Lys Ala Glu Glu Arg Val Leu Lys Lys
    -105                -100                -95
gtc agg agg aaa atc cgt aac aag cag tca gct cag gac agt cgg cgg      782
Val Arg Arg Lys Ile Arg Asn Lys Gln Ser Ala Gln Asp Ser Arg Arg
-90                 -85                 -80                 -75
cgg aag aag gag tac att gat ggg ctg gag agc agg gtg gca gcc tgt      830
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Arg Lys Lys Glu Tyr Ile Asp Gly Leu Glu Ser Arg Val Ala Ala Cys
                -70                 -65                 -60
tct gca cag aac caa gaa tta cag aaa aaa gtc cag gag ctg gag agg      878
Ser Ala Gln Asn Gln Glu Leu Gln Lys Lys Val Gln Glu Leu Glu Arg
            -55                 -50                 -45
cac aac atc tcc ttg gta gct cag ctc cgc cag ctg cag acg cta att      926
His Asn Ile Ser Leu Val Ala Gln Leu Arg Gln Leu Gln Thr Leu Ile
        -40                 -35                 -30
gct caa act tcc aac aaa gct gcc cag acc agc act tgt gtt ttg att      974
Ala Gln Thr Ser Asn Lys Ala Ala Gln Thr Ser Thr Cys Val Leu Ile
    -25                 -20                 -15
ctt ctt ttt tcc ctg gct ctc atc atc ctg ccc agc ttc agt cca ttc     1022
Leu Leu Phe Ser Leu Ala Leu Ile Ile Leu Pro Ser Phe Ser Pro Phe
-10                 -5                  1                   5
cag agt cga cca gaa gct ggg tct gag gat tac cag cct cac gga gtg     1070
Gln Ser Arg Pro Glu Ala Gly Ser Glu Asp Tyr Gln Pro His Gly Val
            10                  15                  20
act tcc aga aat atc ctg acc cac aag gac gta aca gaa aat ctg gag     1118
Thr Ser Arg Asn Ile Leu Thr His Lys Asp Val Thr Glu Asn Leu Glu
        25                  30                  35
acc caa gtg gta gag tcc aga ctg agg gag cca cct gga gcc aag gat     1166
Thr Gln Val Val Glu Ser Arg Leu Arg Glu Pro Pro Gly Ala Lys Asp
    40                  45                  50
gca aat ggc tca aca agg aca ctg ctt gag aag atg gga ggg aag cca     1214
Ala Asn Gly Ser Thr Arg Thr Leu Leu Glu Lys Met Gly Gly Lys Pro
55                  60                  65                  70
aga ccc agt ggg cgc atc cgg tcc gtg ctg cat gca gat gag atg         1259
Arg Pro Ser Gly Arg Ile Arg Ser Val Leu His Ala Asp Glu Met
                75                  80                  85
tgagctggaa cagaccttcc tggcccactt cctgatcaca aggaatcctg ggcttcctta   1319
tggctttctt cccactggga ttcctactta ggtgtctgcc ctcaggggtc caaatcactt   1379
caggacaccc caagagatgt cctttagtct ctgcctgagg cctagtctgc atttgtttgc   1439
atatatgaga gggtacctca aatacttctg ttatgtatct gtgattttat ttcttctttg   1499
ggtatagggt tgaggggaaa taagttttga gtgagaaata aacgttttag ctgaaaaaaa   1559
aaaaaaaaa                                                          1568
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<223> Von Heijne matrix
      score 12.3
      seq HILFLLLLPVAAA/QT
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<222> 471..476
<223> polyA_site
<222> 491..506
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gacatccgct attgctactt ctctgctccc ccacagttcc tctggacttc tctggaccac     60
agtcctctgc cagacccctg ccagacccca gtccacc atg atc cat ctg ggt cac     115
                                      Met Ile His Leu Gly His
                                          -15
atc ctc ttc ctg ctt ttg ctc cca gtg gct gca gct cag acg act cca      163
Ile Leu Phe Leu Leu Leu Leu Pro Val Ala Ala Ala Gln Thr Thr Pro
        -10                 -5                  1
gga gag aga tca tca ctc cct gcc ttt tac cct ggc act tca ggc tct      211
Gly Glu Arg Ser Ser Leu Pro Ala Phe Tyr Pro Gly Thr Ser Gly Ser
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5                   10                  15                  20
tgt tcc gga tgt ggg tcc ctc tct ctg ccg ctc ctg gca ggc ctc gtg      259
Cys Ser Gly Cys Gly Ser Leu Ser Leu Pro Leu Leu Ala Gly Leu Val
                25                  30                  35
gct gct gat gcg gtg gca tcg ctg ctc atc gtg ggg gcg gtg ttc ctg      307
Ala Ala Asp Ala Val Ala Ser Leu Leu Ile Val Gly Ala Val Phe Leu
            40                  45                  50
tgc gca cgc cca cgc cgc agc ccc gcc caa gaa tat ggc aaa gtc tac      355
Cys Ala Arg Pro Arg Arg Ser Pro Ala Gln Glu Tyr Gly Lys Val Tyr
        55                  60                  65
atc aac atg cca ggc agg ggc tgaccctcct gcagcttgga cctttgactt         406
Ile Asn Met Pro Gly Arg Gly
    70                  75
ctgaccctct catcctggat ggtgtgtggt ggcacaggaa cccccgcccc aacttttgga    466
ttgtaataaa acaattgaaa caccaaaaaa aaaaaaaaaa                          506
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<222> 506..511
<223> polyA_site
<222> 528..542
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gaccttaaga agagctaaac gggctgccac ctgtagctga agagtgcctt aacgccgagg     60
cccacggctc c atg cga gag atg cct gtt cct tct ctg ata aat ttg gca     110
             Met Arg Glu Met Pro Val Pro Ser Leu Ile Asn Leu Ala
                 -20                 -15                 -10
gct tca cgt acc cta agt ttt tgc att tct gac aac cac gtg tcc tca      158
Ala Ser Arg Thr Leu Ser Phe Cys Ile Ser Asp Asn His Val Ser Ser
            -5                  1                   5
cct gga ccc gcc aac cca tcc tgt ggc ctc cac cct cac tgg ctt cgt      206
Pro Gly Pro Ala Asn Pro Ser Cys Gly Leu His Pro His Trp Leu Arg
    10                  15                  20
cca ctt aaa ctt tta acg tac aca tgt aga gag ctg aaa ctc cag ggg      254
Pro Leu Lys Leu Leu Thr Tyr Thr Cys Arg Glu Leu Lys Leu Gln Gly
25                  30                  35                  40
taacatggga caggtcctct tgatttaatg aaaacagaag atcaactgga ccgggtagca    314
agaaataagg cttaagaagc actggtttct ctgcagaaga cagcaagatg ccccagggaa    374
tgtttgtgaa aaaggatgac tggatgggaa gcaagctgaa gaaaaagaag gaaagaaaga    434
gagaaatcag taaatcacca cacaagaggt ggagaagagg acttataaat attgtttcta    494
tgacatttga aaataaatgt tttactccat gctaaaaaaa aaaaaaaa                 542
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<222> 148..1140
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<222> 148..240
<223> Von Heijne matrix
      score 10
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seq LVLLLVTRSPVNA/CL
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<222> 1614..1629
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cttggaccct ccccctcgct tctcgttcta ctgccccagg agcccggcgg gtccgggact     120
cccgtccgtg ccggtgcggg cgccggc atg tgg ctg tgg gag gac cag ggc ggc     174
                               Met Trp Leu Trp Glu Asp Gln Gly Gly
                                 -30                 -25
ctc ctg ggc cct ttc tcc ttc ctg ctg cta gtg ctg ctg ctg gtg acg       222
Leu Leu Gly Pro Phe Ser Phe Leu Leu Leu Val Leu Leu Leu Val Thr
        -20                 -15                 -10
cgg agc ccg gtc aat gcc tgc ctc ctc acc ggc agc ctc ttc gtt cta       270
Arg Ser Pro Val Asn Ala Cys Leu Leu Thr Gly Ser Leu Phe Val Leu
    -5                  1                   5                   10
ctg cgc gtc ttc agc ttt gag ccg gtg ccc tct tgc agg gcc ctg cag       318
Leu Arg Val Phe Ser Phe Glu Pro Val Pro Ser Cys Arg Ala Leu Gln
                15                  20                  25
gtg ctc aag ccc cgg gac cgc att tct gcc atc gcc cac cgt ggc ggc       366
Val Leu Lys Pro Arg Asp Arg Ile Ser Ala Ile Ala His Arg Gly Gly
            30                  35                  40
agc cac gac gcg ccc gag aac acg ctg gcg gcc att cgg cag gca gct       414
Ser His Asp Ala Pro Glu Asn Thr Leu Ala Ala Ile Arg Gln Ala Ala
        45                  50                  55
aag aat gga gca aca ggc gtg gag ttg gac att gag ttt act tct gac       462
Lys Asn Gly Ala Thr Gly Val Glu Leu Asp Ile Glu Phe Thr Ser Asp
    60                  65                  70
ggg att cct gtc tta atg cac gat aac aca gta gat agg acg act gat       510
Gly Ile Pro Val Leu Met His Asp Asn Thr Val Asp Arg Thr Thr Asp
75                  80                  85                  90
ggg act ggg cga ttg tgt gat ttg aca ttt gaa caa att agg aag ctg       558
Gly Thr Gly Arg Leu Cys Asp Leu Thr Phe Glu Gln Ile Arg Lys Leu
                95                  100                 105
aat cct gca gca aac cac aga ctc agg aat gat ttc cct gat gaa aag       606
Asn Pro Ala Ala Asn His Arg Leu Arg Asn Asp Phe Pro Asp Glu Lys
            110                 115                 120
atc cct acc cta atg gaa gct gtt gca gag tgc cta aac cat aac ctc       654
Ile Pro Thr Leu Met Glu Ala Val Ala Glu Cys Leu Asn His Asn Leu
        125                 130                 135
aca atc ttc ttt gat gtc aaa ggc cat gca cac aag gct act gag gct       702
Thr Ile Phe Phe Asp Val Lys Gly His Ala His Lys Ala Thr Glu Ala
    140                 145                 150
cta aag aaa atg tat atg gaa ttt cct caa ctg tat aat aat agt gtg       750
Leu Lys Lys Met Tyr Met Glu Phe Pro Gln Leu Tyr Asn Asn Ser Val
155                 160                 165                 170
gtc tgt tct ttc ttg cca gaa gtt atc tac aag atg aga caa aca gat       798
Val Cys Ser Phe Leu Pro Glu Val Ile Tyr Lys Met Arg Gln Thr Asp
                175                 180                 185
cgg gat gta ata aca gca tta act cac aga cct tgg agc cta agc cat       846
Arg Asp Val Ile Thr Ala Leu Thr His Arg Pro Trp Ser Leu Ser His
            190                 195                 200
aca gga gat ggg aaa cca cgc tat gat act ttc tgg aaa cat ttt ata       894
Thr Gly Asp Gly Lys Pro Arg Tyr Asp Thr Phe Trp Lys His Phe Ile
        205                 210                 215
ttt gtt atg atg gac att ttg ctc gat tgg agc atg cat aat atc ttg       942
Phe Val Met Met Asp Ile Leu Leu Asp Trp Ser Met His Asn Ile Leu
    220                 225                 230
tgg tac ctg tgt gga att tca gct ttc ctc atg caa aag gat ttt gta       990
Trp Tyr Leu Cys Gly Ile Ser Ala Phe Leu Met Gln Lys Asp Phe Val
```

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235                 240                 245                 250
tcc ccg gcc tac ttg aag aag tgg tca gct aaa gga atc cag gtt gtt     1038
Ser Pro Ala Tyr Leu Lys Lys Trp Ser Ala Lys Gly Ile Gln Val Val
                255                 260                 265
ggt tgg act gtt aat acc ttt gat gaa aag agt tac tac gaa tcc cat     1086
Gly Trp Thr Val Asn Thr Phe Asp Glu Lys Ser Tyr Tyr Glu Ser His
            270                 275                 280
ctt ggt tcc agc tat atc act gac agc atg gta gaa gac tgc gaa cct     1134
Leu Gly Ser Ser Tyr Ile Thr Asp Ser Met Val Glu Asp Cys Glu Pro
        285                 290                 295
cac ttc tagactttca cggtgggacg aaacgggttc agaaactgcc aggggcctca      1190
His Phe
    300
tacagggata tcaaaatacc ctttgtgcta gcccaggccc tggggaatca ggtgactcac   1250
acaaatgcaa tagttggtca ctgcattttt acctgaacca aagctaaacc cggtgttgcc   1310
accatgcacc atggcatgcc agagttcaac actgttgctc ttgaaaatct gggtctgaaa   1370
aaacgcacaa gagcccctgc cctgccctag ctgaggcaca cagggagacc cagtgaggat   1430
aagcacagat tgaattgtac aatttgcaga tgcagatgta aatgcatggg acatgcatga   1490
taactcagag ttgacatttt aaaacttgcc acacttattt caaatatttg tactcagcta   1550
tgttaacatg tactgtagac atcaaacttg tggccatact aataaaatta ttaaaaggag   1610
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gagtccacgc agctccccag gcccttcacc agcacagcag cagcaggc atg gca gca     117
                                                  Met Ala Ala
agc gtg gag cag cgc gag ggc acc atc cag gtg cag ggc cag gcc ctc      165
Ser Val Glu Gln Arg Glu Gly Thr Ile Gln Val Gln Gly Gln Ala Leu
    -95                 -90                 -85
ttc ttc cga gag gcc ctg ccc ggc agt ggg cag gct cgc ttc tct gta      213
Phe Phe Arg Glu Ala Leu Pro Gly Ser Gly Gln Ala Arg Phe Ser Val
-80                 -75                 -70                 -65
ctg ctg ctg cat ggt att cgc ttc tcc tcc gag acc tgg cag aac ctg      261
Leu Leu Leu His Gly Ile Arg Phe Ser Ser Glu Thr Trp Gln Asn Leu
                -60                 -55                 -50
ggt aca ctg cac agg ctg gcc cag gct ggc tac cgg gct gtg gcc att      309
Gly Thr Leu His Arg Leu Ala Gln Ala Gly Tyr Arg Ala Val Ala Ile
            -45                 -40                 -35
gac ctg cca ggt ctg ggg cac tcc aag gaa gca gca gcc cct gcc cct      357
Asp Leu Pro Gly Leu Gly His Ser Lys Glu Ala Ala Ala Pro Ala Pro
        -30                 -25                 -20
att ggg gag ctg gcc cct ggc agc ttc ctg gcg gct gtg gtg gat gcc      405
Ile Gly Glu Leu Ala Pro Gly Ser Phe Leu Ala Ala Val Val Asp Ala
    -15                 -10                 -5
ttg gag ctg ggc ccc ccg gtt gtg atc agt cca tca ctg agt ggc atg      453
Leu Glu Leu Gly Pro Pro Val Val Ile Ser Pro Ser Leu Ser Gly Met
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1               5                   10                  15
tac tcc ctg ccc ttc ctc acg gcc cct ggc tcc cag ctc ccg ggc ttt      501
Tyr Ser Leu Pro Phe Leu Thr Ala Pro Gly Ser Gln Leu Pro Gly Phe
            20                  25                  30
gtg cca gtg gcc ccc atc tgc act gac aaa atc aat gct gcc aac tat      549
Val Pro Val Ala Pro Ile Cys Thr Asp Lys Ile Asn Ala Ala Asn Tyr
        35                  40                  45
gcc agt gtg aag act cca gct ctg att gta tat gga gac cag gac ccc      597
Ala Ser Val Lys Thr Pro Ala Leu Ile Val Tyr Gly Asp Gln Asp Pro
    50                  55                  60
atg ggt cag acc agc ttt gag cac ctg aag cag ctg ccc aac cac cgg      645
Met Gly Gln Thr Ser Phe Glu His Leu Lys Gln Leu Pro Asn His Arg
65                  70                  75                  80
gtg ctg atc atg aag ggg gcg ggg cac ccc tgt tac ctg gac aaa cca      693
Val Leu Ile Met Lys Gly Ala Gly His Pro Cys Tyr Leu Asp Lys Pro
                85                  90                  95
gag gag tgg cat aca ggg ctg ctg gac ttc ctg cag ggg ctc cag          738
Glu Glu Trp His Thr Gly Leu Leu Asp Phe Leu Gln Gly Leu Gln
            100                 105                 110
tgaagcccag cactgctgca gggggtgggc tgcctgcctg ctctgagctc tctcttgcac    798
gctctctctt ctctcccagg ctctggctca tgcacatgca acaggtgcgt ctgtctatat    858
gtctgggttc ttgtcttttg tggtctgttt gtcttttcta cctctttctc ttgcagtgat    918
agactgaggg ggtaaaatca agagaaaaaa ctctcaggaa tcaaggaaca taatcctgtg    978
gagggtaatc cattacatga gcttctcctg ttcttccact ttcctgcctg gctttcactc   1038
cttcccctgc tctgcccagc ctttccctcc cacccactcc tacttctgca aatgccctga   1098
aggccagccc ttaccccaac acccacttcc ccacctcctt aggccccaga tacatacatg   1158
cccacatgca cgcttacatg tttagagcca tccttgtttc caaatatgac ccttcgcttg   1218
agggcaactg cataggtaca tctaactctg gactggcatg cacattgtca tgtgcagctt   1278
tgcatataca cacatgcata catgagcctc cacacaagca cttgcacaca tgtggactcc   1338
taaccatgct aacctcactg gctgggaagg tggggacccc atgggccagc ccttgcagga   1398
ggccctttg caaggcttag ggtgtggcca gccctgaaag ctacttggac acaggtttca   1458
gctggcccca gcccagaagt gacccccaga aagggagggc caccgctttg ccccctgctt   1518
ttacccttcc ttctgggtgc tctacacctc aggttaccag gcctgaggca tctcagccaa   1578
gcttgtttcc tgctctgagg cttgtggggt gggagccaga gtggaggtcg gtgaaataaa   1638
gtgatgcaat taaaaaaaaa aaaaaaa                                       1665
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ctgccgacgt gttcttccgg tggcggagcg gcggattagc cttcgcgggg caaa atg       57
                                                            Met
gag ctc gag gcc atg agc aga tat acc agc cca gtg aac cca gct gtc      105
Glu Leu Glu Ala Met Ser Arg Tyr Thr Ser Pro Val Asn Pro Ala Val
    -65                 -60                 -55
ttc ccc cat ctg acc gtg gtg ctt ttg gcc att ggc atg ttc ttc acc      153
Phe Pro His Leu Thr Val Val Leu Leu Ala Ile Gly Met Phe Phe Thr
-50                 -45                 -40                 -35
gcc tgg ttc ttc gtt tac gag gtc acc tct acc aag tac act cgt gat      201
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Ala Trp Phe Phe Val Tyr Glu Val Thr Ser Thr Lys Tyr Thr Arg Asp
                -30                 -25                 -20
atc tat aaa gag ctc ctc atc tcc tta gtg gcc tca ctc ttc atg ggc      249
Ile Tyr Lys Glu Leu Leu Ile Ser Leu Val Ala Ser Leu Phe Met Gly
            -15                 -10                 -5
ttt gga gtc ctc ttc ctg ctg ctc tgg gtt ggc atc tac gtg              291
Phe Gly Val Leu Phe Leu Leu Leu Trp Val Gly Ile Tyr Val
        1               5                   10
tgagcaccca agggtaacaa ccagatggct tcactgaaac ctgcttttgt aaattacttt    351
tttttactgt tgctggaaat gtcccacctg ctgctcataa taaatgcaga tgtataacaa    411
aaaaaaaaaa aaaa                                                     425
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<222> 533..546
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gttgcaccag gcgatgcaag acac atg gca gtc tgg cct gaa gtt tcc caa        51
                          Met Ala Val Trp Pro Glu Val Ser Gln
                          1               5
aac agg ctg act agg ggc cta ctg ctt ccc aac tac cag ctg agg ggg       99
Asn Arg Leu Thr Arg Gly Leu Leu Leu Pro Asn Tyr Gln Leu Arg Gly
10                  15                  20                  25
tcc gtc ccg aaa agg gag aag agg cct aag agg aaa cat caa cat ctt      147
Ser Val Pro Lys Arg Glu Lys Arg Pro Lys Arg Lys His Gln His Leu
                30                  35                  40
ttt act cct agc gag cgg cat tct gtc tgc ctt gat tgt ctt ctg gaa      195
Phe Thr Pro Ser Glu Arg His Ser Val Cys Leu Asp Cys Leu Leu Glu
            45                  50                  55
ata tcg ctt tca ggg aaa caa tgg cga aat gtc atc agt ttc aac tgc      243
Ile Ser Leu Ser Gly Lys Gln Trp Arg Asn Val Ile Ser Phe Asn Cys
        60                  65                  70
ttt tgc act act aag acg ctt ttc tgg gtt aat tagcagcaat acagacaacg    296
Phe Cys Thr Thr Lys Thr Leu Phe Trp Val Asn
    75                  80
atcttttatt caacaacctc tctcgagata ttttaaataa tttctcacac tcgaaaaaca    356
tgcagaagcg actattggca aacctgaaga gggtggaata ccaaatggct gaactggaat    416
attttctagt tagcgagggt ttgagaggtg cgtcaggtct ccagaaattc acctcaaaag    476
cgtacaggat gtaatgccag tggtggaaat cattaaagac actttgagta gattcaaaaa    536
aaaaaaaaaa                                                          546
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Met Ala Ser Leu Gly His Ile
-20 -15
ttg gtt ttc tgt gtg ggt ctc ctc acc atg gcc aag gca gaa agt cca 100
Leu Val Phe Cys Val Gly Leu Leu Thr Met Ala Lys Ala Glu Ser Pro
-10 -5 1
aag gaa cac gac ccg ttc act tac gac tac cag tcc ctg cag atc gga 148
Lys Glu His Asp Pro Phe Thr Tyr Asp Tyr Gln Ser Leu Gln Ile Gly
5 10 15
ggc ctc gtc atc gcc ggg atc ctc ttc atc ctg ggc atc ctc atc gtg 196
Gly Leu Val Ile Ala Gly Ile Leu Phe Ile Leu Gly Ile Leu Ile Val
20 25 30 35
ctg agc aga aga tgc cgg tgc aag ttc aac cag cag cag agg act ggg 244
Leu Ser Arg Arg Cys Arg Cys Lys Phe Asn Gln Gln Gln Arg Thr Gly
40 45 50
gaa ccc gat gaa gag gag gga act ttc cgc agc tcc atc cgc cgt ctg 292
Glu Pro Asp Glu Glu Glu Gly Thr Phe Arg Ser Ser Ile Arg Arg Leu
55 60 65
tcc acc cgc agg cgg tagaaacacc tggagcgatg gaatccggcc aggactcccc 347
Ser Thr Arg Arg Arg
70
tggcacctga catctcccac gctccacctg cgcgcccacc gccccctccg ccgccccttc 407
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tctcaaaaaa aaaagaaa 485
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<223> Von Heijne matrix
score 5.9
seq LTLLGLSLILAGL/IV
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<223> polyA_site
<222> 1382..1394
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ctccgagttg ccacccagga aaaagagggc tcctctggga gatgt atg ctt act ctc 57
Met Leu Thr Leu
tta ggc ctt tca ctc atc ttg gca gga ctt att gtt ggt gga gcc tgc 105
Leu Gly Leu Ser Leu Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys
-10 -5 1 5
att tac aag cac ttc atg ccc aag agc acc att tac cgt gga gag atg 153
Ile Tyr Lys His Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met
10 15 20
tgc ttt ttt gat tct gag gat cct gca aat tcc ctt cgt gga gga gag 201
Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly Gly Glu
25 30 35
cct aac ttc ctg cct gtg act gag gag gct gac att cgt gag gat gac 249
Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile Arg Glu Asp Asp
40 45 50
aac att gca atc att gat gtg cct gtc ccc agt ttc tct gat agt gac 297
Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe Ser Asp Ser Asp
55 60 65 70
cct gca gca att att cat gac ttt gaa aag gga atg act gct tac ctg 345

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Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met Thr Ala Tyr Leu
                75                  80                  85
gac ttg ttg ctg ggg aac tgc tat ctg atg ccc ctc aat act tct att      393
Asp Leu Leu Leu Gly Asn Cys Tyr Leu Met Pro Leu Asn Thr Ser Ile
            90                  95                  100
gtt atg cct cca gaa aat ctg gta gag ctc ttt ggc aaa ctg gcg agt      441
Val Met Pro Pro Glu Asn Leu Val Glu Leu Phe Gly Lys Leu Ala Ser
        105                 110                 115
ggc aga tat ctg cct caa act tat gtg gtt cga gaa gac cta gtt gct      489
Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu Asp Leu Val Ala
    120                 125                 130
gtg gag gaa att cgt gat gtt agt aac ctt ggc atc ttt att tac caa      537
Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile Phe Ile Tyr Gln
135                 140                 145                 150
ctt tgc aat aac aga aag tcc ttc cgc ctt cgt cgc aga gac ctc ttg      585
Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg Arg Asp Leu Leu
                155                 160                 165
ctg ggt ttc aac aaa cgt gcc att gat aaa tgc tgg aag att aga cac      633
Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp Lys Ile Arg His
            170                 175                 180
ttc ccc aac gaa ttt att gtt gag acc aag atc tgt caa gag              675
Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys Gln Glu
        185                 190                 195
taagaggcaa cagatagagt gtccttggta acaagaagtc agagatttac aatatgactt     735
taacattaag gtttatggga tactcaagat atttactcat gcatttactc tattgcttat     795
gctttaaaaa aaggaaaaaa aaaaactact aaccactgca agctcttgtc aaattttagt     855
ttaattggca ttgcttgttt tttgaaactg aaattacctg agtttcattt tttctttgaa     915
tttatagggt ttagatttct gaaagcagca tgaatatatc acctaacatc ctgacaataa     975
attccatccg ttgtttttt tgtttgtttg ttttttcttt tcctttaagt aagctcttta    1035
ttcatcttat ggtgcagcaa ttttaaaatt tgaaatattt taaattgttt ttgaactttt    1095
tgtgtaaaat atatcagatc tcaacattgt tggtttcttt tgtttttcat tttgtacaac    1155
tttcttgaat ttagaaatta catctttgca gctctgttag gtgctctgta attaacctga    1215
cttatatgtg aacaattttc atgagacagt cattttaaa taatgcagtg attctttctc    1275
actactatct gtattgtgga atgcacaaaa ttgtgtaggt gctgaatgct gtaaggagtt    1335
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ccgtggtgag gaaccctgga ctctcagcat cacaagaggc aacaccagga gccaacatga     120
gctcgggact gaactgctgt ggcccggagc agcgctgctg gtgctgttgg gggtggcagc     180
cagtctgtgt gtgcgctgct cacgcccagg tgcaaagagg tcagagagaa tctaccagca     240
gagaagtctg cgtgaggacc aacagagctt tacggggtcc cggacctact ccttggtcgg     300
gcaggcatgg ccaggacccc tggcggac atg gca ccc aca agg aag gac aag        352
                          Met Ala Pro Thr Arg Lys Asp Lys
                                          -135
ctg ttg caa ttc tac ccc agc ctg gag gat cca gca tct tcc agg tac       400
Leu Leu Gln Phe Tyr Pro Ser Leu Glu Asp Pro Ala Ser Ser Arg Tyr
    -130                -125                -120
```

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cag aac ttc agc aaa gga agc aga cac ggg tcg gag gaa gcc tac ata      448
Gln Asn Phe Ser Lys Gly Ser Arg His Gly Ser Glu Glu Ala Tyr Ile
-115                -110                -105                -100
gac ccc att gcc atg gag tat tac aac tgg ggg cgg ttc tcg aag ccc      496
Asp Pro Ile Ala Met Glu Tyr Tyr Asn Trp Gly Arg Phe Ser Lys Pro
                -95                 -90                 -85
cca gaa ggt gag gcg aag gac aaa gcc gga ggt gga gga agt ggt gtg      544
Pro Glu Gly Glu Ala Lys Asp Lys Ala Gly Gly Gly Gly Ser Gly Val
            -80                 -75                 -70
gga gct cag ggc aga agc cat acc tcc agg cag gag agg agg ctg ggc      592
Gly Ala Gln Gly Arg Ser His Thr Ser Arg Gln Glu Arg Arg Leu Gly
        -65                 -60                 -55
ctg ggt tcg gat gat gat gcc aat tcc tac gag aat gtg ctc att tgc      640
Leu Gly Ser Asp Asp Asp Ala Asn Ser Tyr Glu Asn Val Leu Ile Cys
    -50                 -45                 -40
aag cag aaa acc aca gag aca ggt gcc cag cag gag gac gta ggt ggc      688
Lys Gln Lys Thr Thr Glu Thr Gly Ala Gln Gln Glu Asp Val Gly Gly
-35                 -30                 -25                 -20
ctc tgc aga ggg gac ctc agc ctg tca ctg gcc ctg aag act ggc ccc      736
Leu Cys Arg Gly Asp Leu Ser Leu Ser Leu Ala Leu Lys Thr Gly Pro
                -15                 -10                 -5
act tct ggt ctc tgt ccc tct gcc tcc ccg gaa gaa gat ggg gaa tct      784
Thr Ser Gly Leu Cys Pro Ser Ala Ser Pro Glu Glu Asp Gly Glu Ser
            1                   5                   10
gag gat tat cag aac tca gca tcc atc cat caa tgg cgc gag tcc agg      832
Glu Asp Tyr Gln Asn Ser Ala Ser Ile His Gln Trp Arg Glu Ser Arg
    15                  20                  25
aag gtc atg ggg caa ctc cag aga gaa gca tcc cct ggc ccg gtg gga      880
Lys Val Met Gly Gln Leu Gln Arg Glu Ala Ser Pro Gly Pro Val Gly
30                  35                  40                  45
agc cca gac gag gag gac ggg gaa ccg gat tac gtg aat ggg gag gtg      928
Ser Pro Asp Glu Glu Asp Gly Glu Pro Asp Tyr Val Asn Gly Glu Val
                50                  55                  60
gca gcc aca gaa gcc tagggcagac caagaagaaa ggagccaagg caaagagggg      983
Ala Ala Thr Glu Ala
            65
ccactgtgct catggaccca tcgctgcctt ccaaggacca tttcccagag ctactcaact   1043
tttaagcccc tgccatggtt gctcctggaa ggagaaccag ccaccctgag gaccacctgg   1103
ccatgcgtgc acagcctggg aaaagacagt tactcacggg agctgcaggc ccgtcaccaa   1163
gccctctccc gacccaggct ttgtggggca ggcacctggt accatgggta acccggctcc   1223
tggtatggac ggatgcgcag gatttaggat aagctgtcac ccagtcccca taacaaaacc   1283
actgtccaac actggtatct gtgttctttt gtgctatgaa aaaaaaaaaa              1333
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                          Met Lys Lys Val Leu Leu Leu Ile Thr
                                -15                 -10
gcc atc ttg gca gtg gct gtt ggt ttc cca gtc tct caa gac cag gaa      101
Ala Ile Leu Ala Val Ala Val Gly Phe Pro Val Ser Gln Asp Gln Glu
            -5                  1                   5
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cga gaa aaa aga agt atc agt gac agc gat gaa tta gct tca ggg ttt      149
Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly Phe
    10                  15                  20
ttt gtg ttc cct tac cca tat cca ttt cgc cca ctt cca cca att cca      197
Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile Pro
25                  30                  35                  40
ttt cca aga ttt cca tgg ttt aga cgt aat ttt cct att cca ata cct      245
Phe Pro Arg Phe Pro Trp Phe Arg Arg Asn Phe Pro Ile Pro Ile Pro
                45                  50                  55
gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaagaa           291
Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys
            60                  65
ggaaaagtca cgataaacct ggtcacctga aattg                               326
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<222> 692..703
<400> 79
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atg caa gct cag gcg ccg gtg gtc gtt gtg acc caa cct gga gtc ggt      108
Met Gln Ala Gln Ala Pro Val Val Val Val Thr Gln Pro Gly Val Gly
    -50                 -45                 -40
ccc ggt ccg gcc ccc cag aac tcc aac tgg cag aca ggc atg tgt gac      156
Pro Gly Pro Ala Pro Gln Asn Ser Asn Trp Gln Thr Gly Met Cys Asp
-35                 -30                 -25                 -20
tgt ttc agc gac tgc gga gtc tgt ctc tgt ggc aca ttt tgt ttc ccg      204
Cys Phe Ser Asp Cys Gly Val Cys Leu Cys Gly Thr Phe Cys Phe Pro
                -15                 -10                 -5
tgc ctt ggg tgt caa gtt gca gct gat atg aat gaa tgc tgt ctg tgt      252
Cys Leu Gly Cys Gln Val Ala Ala Asp Met Asn Glu Cys Cys Leu Cys
            1                   5                   10
gga aca agc gtc gca atg agg act ctc tac agg acc cga tat ggc atc      300
Gly Thr Ser Val Ala Met Arg Thr Leu Tyr Arg Thr Arg Tyr Gly Ile
    15                  20                  25
cct gga cct att tgt gat gac tat atg gca act ctt tgc tgt cct cat      348
Pro Gly Pro Ile Cys Asp Asp Tyr Met Ala Thr Leu Cys Cys Pro His
30                  35                  40                  45
tgt act ctt tgc caa atc aag aga gat atc aac aga agg aga gcc atg      396
Cys Thr Leu Cys Gln Ile Lys Arg Asp Ile Asn Arg Arg Arg Ala Met
                50                  55                  60
cgt act ttc taaaaactga tggtgaaaag ctcttaccga agcaacaaaa               445
Arg Thr Phe
ttcagcagac acctctccag cttgagttct tcaccatctt ttgcaactga aatatgatgg     505
atatgcttaa gtacaactga tggcatgaaa aaaatcaaat ttttgattta ttataaatga     565
atgttgtccc tgaacttagc taaatggtgc aacttagttt ctccttgctt tcatattatc     625
gaatttcctg gcttataaac tttttaaatt acatttgaaa tataaaccaa atgaaatatt     685
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cccttagtag agcgga atg agt aat acc cac acg gtg ctt gtc tca ctt ccc 172
Met Ser Asn Thr His Thr Val Leu Val Ser Leu Pro
-30 -25 -20
cat ccg cac ccg gcc ctc acc tgc tgt cac ctc ggc ctc cca cac ccg 220
His Pro His Pro Ala Leu Thr Cys Cys His Leu Gly Leu Pro His Pro
-15 -10 -5
gtc cgc gct ccc cgc cct ctt cct cgc gta gaa ccg tgg gat cct agg 268
Val Arg Ala Pro Arg Pro Leu Pro Arg Val Glu Pro Trp Asp Pro Arg
1 5 10
tgg cag gac tca gag cta agg tat cca cag gcc atg aat tcc ttc cta 316
Trp Gln Asp Ser Glu Leu Arg Tyr Pro Gln Ala Met Asn Ser Phe Leu
15 20 25
aat gag cgg tca tcg ccg tgc agg acc tta agg caa gaa gca tcg gct 364
Asn Glu Arg Ser Ser Pro Cys Arg Thr Leu Arg Gln Glu Ala Ser Ala
30 35 40 45
gac aga tgt gat ctc tgaacctgat agattgctga ttttatctta ttttatcctt 419
Asp Arg Cys Asp Leu
50
gacttggtac aagttttggg atttctgaaa agaccatgca gataaccaca aatatcaaga 479
aagtcgtctt cagtattaag tagaatttag atttaggttt ccttcctgct tcccacctcc 539
ttcgaataag gaaacgtctt tgggaccaac tttatggaat aaataagctg agctgtattt 599
caagtaatat agttataaat taacaatgta gcagttattg atagagaaat tgagaaaact 659
gaaacgtgac cggagtattg gaaataacgt agtacatcac ctagcacaat gacacatagt 719
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score 7.2
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<223> polyA_site
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Met Gly Thr Ala Asp Ser
-35

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gat gag atg gcc ccg gag gcc cca cag cac acc cac atc gat gtg cac      102
Asp Glu Met Ala Pro Glu Ala Pro Gln His Thr His Ile Asp Val His
            -30                 -25                 -20
atc cac cag gag tct gcc ctg gcc aag ctc ctg ctc acc tgc tgc tct      150
Ile His Gln Glu Ser Ala Leu Ala Lys Leu Leu Leu Thr Cys Cys Ser
        -15                 -10                 -5
gcg ctg cgg ccc cgg gcc acc cag gcc agg ggc agc agc cgg ctg ctg      198
Ala Leu Arg Pro Arg Ala Thr Gln Ala Arg Gly Ser Ser Arg Leu Leu
    1               5                   10                  15
gtg gcc tcg tgg gtg atg cag atc gtg ctg ggg atc ttg agt gca gtc      246
Val Ala Ser Trp Val Met Gln Ile Val Leu Gly Ile Leu Ser Ala Val
                20                  25                  30
cta gga gga ttt ttc tac atc cgc gac tac acc ctc ctc gtc acc tcg      294
Leu Gly Gly Phe Phe Tyr Ile Arg Asp Tyr Thr Leu Leu Val Thr Ser
            35                  40                  45
ggg gct gcc atc tgg aca ggg gct gtg gct gtg ctg gct gga gct gct      342
Gly Ala Ala Ile Trp Thr Gly Ala Val Ala Val Leu Ala Gly Ala Ala
        50                  55                  60
gcc ttc att tac gag aaa cgg ggt ggt aca tac tgg gcc ctg ctg agg      390
Ala Phe Ile Tyr Glu Lys Arg Gly Gly Thr Tyr Trp Ala Leu Leu Arg
    65                  70                  75
act ctg cta gcg ctg gca gct ttc tcc aca gcc atc gct gcc ctc aaa      438
Thr Leu Leu Ala Leu Ala Ala Phe Ser Thr Ala Ile Ala Ala Leu Lys
80                  85                  90                  95
ctt tgg aat gaa gat ttc cga tat ggc tac tct tat tac aac agt gcc      486
Leu Trp Asn Glu Asp Phe Arg Tyr Gly Tyr Ser Tyr Tyr Asn Ser Ala
                100                 105                 110
tgc cgc atc tcc agc tcg agt gac tgg aac act cca gcc ccc act cag      534
Cys Arg Ile Ser Ser Ser Ser Asp Trp Asn Thr Pro Ala Pro Thr Gln
            115                 120                 125
agt cca gaa gaa gtc aga agg cta cac cta tgt acc tcc ttc atg gac      582
Ser Pro Glu Glu Val Arg Arg Leu His Leu Cys Thr Ser Phe Met Asp
        130                 135                 140
atg ctg aag gcc ttg ttc aga acc ctt cag gcc atg ctc ttg ggt gtc      630
Met Leu Lys Ala Leu Phe Arg Thr Leu Gln Ala Met Leu Leu Gly Val
    145                 150                 155
tgg att ctg ctg ctt ctg gca tct ctg gcc cct ctg tgg ctg tac tgc      678
Trp Ile Leu Leu Leu Leu Ala Ser Leu Ala Pro Leu Trp Leu Tyr Cys
160                 165                 170                 175
tgg aga atg ttc cca acc aaa ggg aaa aga gac cag aag gaa atg ttg      726
Trp Arg Met Phe Pro Thr Lys Gly Lys Arg Asp Gln Lys Glu Met Leu
                180                 185                 190
gaa gtg agt gga atc tagccatgcc tctcctgatt attagtgcct ggtgcttctg      781
Glu Val Ser Gly Ile
            195
caccgggcgt ccctgcatct gactgctgga agaagaacca gactgaggaa aagaggctct    841
tcaacagccc cagttatcct ggccccatga ccgtggccac agccctgctc cagcagcact    901
tgcccattcc ttacacccct tccccatcct gctccgcttc atgtcccctc ctgagtagtc    961
atgtgataat aaactctcat gttattgttc ccaaaaaaaa aaaaaa                   1007
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      seq TFCLIFGLGAVWG/LG
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gactgagctg atccgcacc atg gag tct cgg gtc tta ctg aga aca ttc tgt 112
Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys
-20 -15
ttg atc ttc ggt ctc gga gca gtt tgg ggg ctt ggt gtg gac cct tcc 160
Leu Ile Phe Gly Leu Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser
-10 -5 1 5
cta cag att gac gtc tta aca gag tta gaa ctt ggg gag tcc acg acc 208
Leu Gln Ile Asp Val Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr
10 15 20
gga gtg cgt cag gtc ccg ggg ctg cat aat ggg acg aaa gcc ttt ctc 256
Gly Val Arg Gln Val Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu
25 30 35
ttt caa gcg tgactgaagc agcagcctgc acatgtggat ggtcatcagt 305
Phe Gln Ala
40
gcctcgccca gagatacctg gccttcatcc aaagggaccc tgctgccaca agtcctccag 365
gcagcacccg cactgtggct ccttcgcact gagtatgttg gactctgcca tagactgacc 425
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ggataaataa aaacaaacaa atgcttctgt caaaaaaaaa aa 527
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tgttggccta tcatggggca tgccatgggg ctggtccttt ccctaccggt tcactgcttg 180
accttcgcct cctcagcacc ttcaagcccc cagcctacga ggatgtggtt caccgcccag 240
gcacaccacc ccccccttat actgtggccc caggccgccc cttgactgct tccagtgaac 300
aaacctgctg ttcctcctca tccagctgcc ctgcccactt tgaaggaaca aatgtggaag 360
gtgtttcctc ccaccagagt gccccccctc atcaggaggg tgagcccggg gcaggggtga 420
cccctgcctc cacacccccc tcctgccgct atcgccgttt aactggcgac tccggtattg 480
agctctgccc ttgtcctgcc tccggtgagg gtgagccagt caaggaggtg agggttagtg 540
ccaccctgcc agatctggag gactactccc cgtgtgcact acccccagag tctgtaccgc 600
agatctttcc c atg ggg ctg tct tcc agt gaa ggg gac atc cca 644
Met Gly Leu Ser Ser Ser Glu Gly Asp Ile Pro
1 5 10
taagtagttt tgagagggtg gatgggttac ttgcccacca gaaacagccc tagtcccaac 704
tccttgcgtt cctttggccc ctccctgcct acctagaatc tgcctgaagg ggctggagag 764
ggacagtatt gggggactgt gctagcttta cccccgcagg acatacacag gagcctttga 824
tctcattaaa gagatgtaaa ccagcaaaaa aaaaaaa 861
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score 4
seq IAVLYLHLYDVFG/DP
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atg gag aga ggc ctg aaa tca gca gac cct cgg gat ggc acc ggt tac 108
Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr
-30 -25 -20
act ggc tgg gca ggt att gct gtg ctt tac tta cat ctt tat gat gta 156
Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val
-15 -10 -5
ttt ggg gac cct gcc tct atg ttc tgt aaa gta ttt gac tta cta gtt 204
Phe Gly Asp Pro Ala Ser Met Phe Cys Lys Val Phe Asp Leu Leu Val
1 5 10
ctc aat aaa att tta tta gga cta taaaaaaaaa a 239
Leu Asn Lys Ile Leu Leu Gly Leu
15 20
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<400> 85
Met His Arg Pro Glu Ala Met Leu Leu Leu Leu Thr Leu Ala Leu Leu
-20 -15 -10
Gly Gly Pro Thr Trp Ala Gly Lys Met Tyr Gly Pro Gly Gly Gly Lys
-5 1 5 10
Tyr Phe Ser Thr Thr Glu Asp Tyr Asp His Glu Ile Thr Gly Leu Arg
15 20 25
Val Ser Val Gly Leu Leu Leu Val Lys Ser Val Gln Val Lys Leu Gly
30 35 40
Asp Ser Trp Asp Val Lys Leu Gly Ala Leu Gly Gly Asn Thr Gln Glu
45 50 55
Val Thr Leu Gln Pro Gly Glu Tyr Ile Thr Lys Val Phe Val Ala Phe
60 65 70
Gln Thr Phe Leu Arg Gly Met Val Met Tyr Thr Ser Lys Asp Arg Tyr
75 80 85 90
Phe Tyr Phe Gly Lys Leu Asp Gly Gln Ile Ser Ser Ala Tyr Pro Ser
95 100 105
Gln Glu Gly Gln Val Leu Val Gly Ile Tyr Gly Gln Tyr Gln Leu Leu
110 115 120
Gly Ile Lys Ser Ile Gly Phe Glu Trp Asn Tyr Pro Leu Glu Glu Pro
125 130 135
Thr Thr Glu Pro Pro Val Asn Leu Thr Tyr Ser Ala Asn Ser Pro Val
140 145 150
Gly Arg
155
<210> 86
<211> 90
<212> PRT
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<223> SIGNAL
<222> -19..-1
<400> 86

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Met Lys Phe Leu Ala Val Leu Val Leu Leu Gly Val Ser Ile Phe Leu
                -15                 -10                  -5
Val Ser Ala Gln Asn Pro Thr Thr Ala Ala Pro Ala Asp Thr Tyr Pro
            1                   5                   10
Ala Thr Gly Pro Ala Asp Asp Glu Ala Pro Asp Ala Glu Thr Thr Ala
    15                  20                  25
Ala Ala Thr Thr Ala Thr Thr Ala Ala Pro Thr Thr Ala Thr Thr Ala
30                  35                  40                  45
Ala Ser Thr Thr Ala Arg Lys Asp Ile Pro Val Leu Pro Lys Trp Val
                50                  55                  60
Gly Asp Leu Pro Asn Gly Arg Val Cys Pro
            65                  70
<210> 87
<211> 125
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -15..-1
<400> 87
Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
-15                 -10                  -5                   1
Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
            5                   10                  15
Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
        20                  25                  30
Val Glu Trp Ser Ala Phe Leu Glu Ala Ala Asp Asn Leu Arg Leu Ile
    35                  40                  45
Gln Val Pro Lys Gly Pro Val Glu Gly Tyr Glu Glu Asn Glu Glu Phe
50                  55                  60                  65
Leu Arg Thr Met His His Leu Leu Leu Glu Val Glu Val Ile Glu Gly
                70                  75                  80
Thr Leu Gln Cys Pro Glu Ser Gly Arg Met Phe Pro Ile Ser Arg Gly
            85                  90                  95
Ile Pro Asn Met Leu Leu Ser Glu Glu Glu Thr Glu Ser
        100                 105                 110
<210> 88
<211> 136
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -34..-1
<400> 88
Met Leu Phe Ser Leu Arg Glu Leu Val Gln Trp Leu Gly Phe Ala Thr
                -30                 -25                 -20
Phe Glu Ile Phe Val His Leu Leu Ala Leu Leu Val Phe Ser Val Leu
            -15                 -10                  -5
Leu Ala Leu Arg Val Asp Gly Leu Val Pro Gly Leu Ser Trp Trp Asn
        1                   5                   10
Val Phe Val Pro Phe Phe Ala Ala Asp Gly Leu Ser Thr Tyr Phe Thr
15                  20                  25                  30
Thr Ile Val Ser Val Arg Leu Phe Gln Asp Gly Glu Lys Arg Leu Ala
                35                  40                  45
Val Leu Arg Leu Phe Trp Val Leu Thr Val Leu Ser Leu Lys Phe Val
            50                  55                  60
Phe Glu Met Leu Leu Cys Gln Lys Leu Ala Glu Gln Thr Arg Glu Leu
        65                  70                  75
Trp Phe Gly Leu Ile Thr Ser Pro Leu Phe Ile Leu Leu Gln Leu Leu
    80                  85                  90
Met Ile Arg Ala Cys Arg Val Asn
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95 100
<210> 89
<211> 238
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -53..-1
<400> 89
Met Ala Asp Pro Asp Pro Arg Tyr Pro Arg Ser Ser Ile Glu Asp Asp
-50 -45 -40
Phe Asn Tyr Gly Ser Ser Val Ala Ser Ala Thr Val His Ile Arg Met
-35 -30 -25
Ala Phe Leu Arg Lys Val Tyr Ser Ile Leu Ser Leu Gln Val Leu Leu
-20 -15 -10
Thr Thr Val Thr Ser Thr Val Phe Leu Tyr Phe Glu Ser Val Arg Thr
-5 1 5 10
Phe Val His Glu Ser Pro Ala Leu Ile Leu Leu Phe Ala Leu Gly Ser
15 20 25
Leu Gly Leu Ile Phe Ala Leu Ile Leu Asn Arg His Lys Tyr Pro Leu
30 35 40
Asn Leu Tyr Leu Leu Phe Gly Phe Thr Leu Leu Glu Ala Leu Thr Val
45 50 55
Ala Val Val Val Thr Phe Tyr Asp Val Tyr Ile Ile Leu Gln Ala Phe
60 65 70 75
Ile Leu Thr Thr Thr Val Phe Phe Gly Leu Thr Val Tyr Thr Leu Gln
80 85 90
Ser Lys Lys Asp Phe Ser Lys Phe Gly Ala Gly Leu Phe Ala Leu Leu
95 100 105
Trp Ile Leu Cys Leu Ser Gly Phe Leu Lys Phe Phe Leu Tyr Ser Glu
110 115 120
Ile Met Glu Leu Val Leu Ala Ala Ala Gly Ala Leu Leu Phe Cys Gly
125 130 135
Phe Ile Ile Tyr Asp Thr His Ser Leu Met His Lys Leu Ser Pro Glu
140 145 150 155
Glu Tyr Val Leu Ala Ala Ile Ser Leu Tyr Leu Asp Ile Ile Asn Leu
160 165 170
Phe Leu His Leu Leu Arg Phe Leu Glu Ala Val Asn Lys Lys
175 180 185
<210> 90
<211> 106
<212> PRT
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Met Ser Thr Asn Asn Met Ser Asp Pro Arg Arg Pro Asn Lys Val Leu
-70 -65 -60
Arg Tyr Lys Pro Pro Pro Ser Glu Cys Asn Pro Ala Leu Asp Asp Pro
-55 -50 -45 -40
Thr Pro Asp Tyr Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly
-35 -30 -25
Leu Met Leu Lys Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser
-20 -15 -10
Phe Ile Ser Phe Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met
-5 1 5
Met Ser Ser Phe Met Leu Ser Ile Ser Ala Val Val Met Ser Tyr Leu
10 15 20 25
Gln Asn Pro Gln Pro Met Thr Pro Pro Trp
30 35

<210> 91
<211> 123
<212> PRT
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<400> 91
Met Ser Gly Gly Pro Glu Ala Arg Pro Pro Met Leu Val Glu Gly Gly
-80 -75 -70
Gly Pro Glu Ser Leu Gln Lys Ala Pro Cys Thr Arg Gly Pro Pro Ser
-65 -60 -55
His Pro Val Pro Pro Ala Leu Ala Phe Thr Val Gly Asn Gly Ser Gly
-50 -45 -40
Pro Gly Val Arg Cys Pro Arg Asn Met Ala Glu Gly His Pro Gly Pro
-35 -30 -25
Glu Arg Arg Gln Ser Gln Gln Gly Leu Phe Arg Ala Ala Trp Leu Pro
-20 -15 -10 -5
Gly Ser Arg Pro Ser Pro Leu Phe Cys Val Cys Ser Val Thr Ser Pro
1 5 10
Gly Trp Asp Val Pro Gln Val His Arg Val Glu Val Gly His Gly Arg
15 20 25
Arg Gln Glu Thr His Pro Val Arg Arg Arg Ala
30 35
<210> 92
<211> 75
<212> PRT
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<400> 92
Met Pro Arg Gly Arg Arg Leu Gly Met Val Phe Ala Pro Pro Arg Pro
-45 -40 -35
Gly Gln Arg Gln Ala Gly Ala Pro Trp Val Pro Glu Arg Arg Lys Arg
-30 -25 -20
Arg Pro Asp Gly Asp Thr Phe Leu Leu Ser Phe Leu Ser Thr Thr Trp
-15 -10 -5
Leu Lys Thr Trp Arg Ser Gln Gln Tyr Lys Glu Ser Lys Ser Arg Ser
1 5 10 15
Cys Ala Arg Glu Gln Met Asn Ser Ser Ser Cys
20 25
<210> 93
<211> 80
<212> PRT
<213> Homo sapiens
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<222> -40..-1
<400> 93
Met Asp Gly Ile Pro Met Ser Met Lys Asn Glu Met Pro Ile Ser Gln
-40 -35 -30 -25
Leu Leu Met Ile Ile Ala Pro Ser Leu Gly Phe Val Leu Phe Ala Leu
-20 -15 -10
Phe Val Ala Phe Leu Leu Arg Gly Lys Leu Met Glu Thr Tyr Cys Ser
-5 1 5
Gln Lys His Thr Arg Leu Asp Tyr Ile Gly Asp Ser Lys Asn Val Leu
10 15 20
Asn Asp Val Gln His Gly Arg Glu Asp Glu Asp Gly Leu Phe Thr Leu
25 30 35 40
<210> 94

<211> 327
<212> PRT
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<223> SIGNAL
<222> -49..-1
<400> 94

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Met Phe Pro Ser Arg Arg Lys Ala Ala Gln Leu Pro Trp Glu Asp Gly
                -45                 -40                 -35
Arg Ser Gly Leu Leu Ser Gly Gly Leu Pro Arg Lys Cys Ser Val Phe
            -30                 -25                 -20
His Leu Phe Val Ala Cys Leu Ser Leu Gly Phe Phe Ser Leu Leu Trp
        -15                 -10                 -5
Leu Gln Leu Ser Cys Ser Gly Asp Val Ala Arg Ala Val Arg Gly Gln
    1               5                   10                  15
Gly Gln Glu Thr Ser Gly Pro Pro Arg Ala Cys Pro Pro Glu Pro Pro
                20                  25                  30
Pro Glu His Trp Glu Glu Asp Ala Ser Trp Gly Pro His Arg Leu Ala
            35                  40                  45
Val Leu Val Pro Phe Arg Glu Arg Phe Glu Glu Leu Leu Val Phe Val
        50                  55                  60
Pro His Met Arg Arg Phe Leu Ser Arg Lys Lys Ile Arg His His Ile
    65                  70                  75
Tyr Val Leu Asn Gln Val Asp His Phe Arg Phe Asn Arg Ala Ala Leu
80                  85                  90                  95
Ile Asn Val Gly Phe Leu Glu Ser Ser Asn Ser Thr Asp Tyr Ile Ala
                100                 105                 110
Met His Asp Val Asp Leu Leu Pro Leu Asn Glu Glu Leu Asp Tyr Gly
            115                 120                 125
Phe Pro Glu Ala Gly Pro Phe His Val Ala Ser Pro Glu Leu His Pro
        130                 135                 140
Leu Tyr His Tyr Lys Thr Tyr Val Gly Gly Ile Leu Leu Leu Ser Lys
    145                 150                 155
Gln His Tyr Arg Leu Cys Asn Gly Met Ser Asn Arg Phe Trp Gly Trp
160                 165                 170                 175
Gly Arg Glu Asp Asp Glu Phe Tyr Arg Arg Ile Lys Gly Ala Gly Leu
                180                 185                 190
Gln Leu Phe Arg Pro Ser Gly Ile Thr Thr Gly Tyr Lys Thr Phe Arg
            195                 200                 205
His Leu His Asp Pro Ala Trp Arg Lys Arg Asp Gln Lys Arg Ile Ala
        210                 215                 220
Ala Gln Lys Gln Glu Gln Phe Lys Val Asp Arg Glu Gly Gly Leu Asn
    225                 230                 235
Thr Val Lys Tyr His Val Ala Ser Arg Thr Ala Leu Ser Val Gly Gly
240                 245                 250                 255
Ala Pro Cys Thr Val Leu Asn Ile Met Leu Asp Cys Asp Lys Thr Ala
                260                 265                 270
Thr Pro Trp Cys Thr Phe Ser
            275
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<211> 235
<212> PRT
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<220>
<223> SIGNAL
<222> -20..-1
<400> 95

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-20                 -15                 -10                 -5
Ala Ser Leu Cys Ala Trp Tyr Ser Gly Tyr Leu Leu Ala Glu Leu Ile
                1                   5                   10
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Pro Asp Ala Pro Leu Ser Ser Ala Ala Tyr Ser Ile Arg Ser Ile Gly
        15                  20                  25
Glu Arg Pro Val Leu Lys Ala Pro Val Pro Lys Arg Gln Lys Cys Asp
    30                  35                  40
His Trp Thr Pro Cys Pro Ser Asp Thr Tyr Ala Tyr Arg Leu Leu Ser
45                  50                  55                  60
Gly Gly Gly Arg Ser Lys Tyr Ala Lys Ile Cys Phe Glu Asp Asn Leu
                65                  70                  75
Leu Met Gly Glu Gln Leu Gly Asn Val Ala Arg Gly Ile Asn Ile Ala
            80                  85                  90
Ile Val Asn Tyr Val Thr Gly Asn Val Thr Ala Thr Arg Cys Phe Asp
        95                  100                 105
Met Tyr Glu Gly Asp Asn Ser Gly Pro Met Thr Lys Phe Ile Gln Ser
    110                 115                 120
Ala Ala Pro Lys Ser Leu Leu Phe Met Val Thr Tyr Asp Asp Gly Ser
125                 130                 135                 140
Thr Arg Leu Asn Asn Asp Ala Lys Asn Ala Ile Glu Ala Leu Gly Ser
                145                 150                 155
Lys Glu Ile Arg Asn Met Lys Phe Arg Ser Ser Trp Val Phe Ile Ala
            160                 165                 170
Ala Lys Gly Leu Glu Leu Pro Ser Glu Ile Gln Arg Glu Lys Ile Asn
        175                 180                 185
His Ser Asp Ala Lys Asn Asn Arg Tyr Ser Gly Trp Pro Ala Glu Ile
    190                 195                 200
Gln Ile Glu Gly Cys Ile Pro Lys Glu Arg Ser
205                 210                 215
<210> 96
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    -30                 -25                 -20
Ser Tyr Val Leu Phe Ser Ala Ser Ser Phe Pro Ser Ile Ser Gly Asn
-15                 -10                 -5                  1
Ile Arg Ser Arg Asn Tyr Phe Gln Lys Gln Asn Asn His Trp Phe Gln
            5                   10                  15
Thr Ser Asp Tyr
        20
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<223> SIGNAL
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<400> 97
Met Gln Asp Glu Asp Gly Tyr Ile Thr Leu Asn Ile Lys Thr Arg Lys
        -45                 -40                 -35
Pro Ala Leu Val Ser Val Gly Pro Ala Ser Ser Phe Trp Trp Arg Val
    -30                 -25                 -20
Met Ala Leu Ile Leu Leu Ile Leu Cys Val Gly Met Val Val Gly Leu
-15                 -10                 -5                  1
Val Ala Leu Gly Ile Trp Ser Val Met Gln Arg Asn Tyr Leu Gln Asp
            5                   10                  15
Glu Asn Glu Asn Arg Thr Gly Thr Leu Gln Gln Leu Ala Lys Arg Phe
        20                  25                  30
Cys Gln Tyr Val Val Lys Gln Ser Glu Leu Lys Gly Thr Phe Lys Gly
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    35                  40                  45
His Lys Cys Ser Pro Cys Asp Thr Asn Trp Arg Tyr Tyr Gly Asp Ser
50                  55                  60                  65
Cys Tyr Gly Phe Phe Arg His Asn Leu Thr Trp Glu Glu Ser Lys Gln
                70                  75                  80
Tyr Cys Thr Asp Met Asn Ala Thr Leu Leu Lys Ile Asp Asn Arg Asn
            85                  90                  95
Ile Val Glu Tyr Ile Lys Ala Arg Thr His Leu Ile Arg Trp Val Gly
        100                 105                 110
Leu Ser Arg Gln Lys Ser Asn Glu Val Trp Lys Trp Glu Asp Gly Ser
    115                 120                 125
Val Ile Ser Glu Asn Met Phe Glu Phe Leu Glu Asp Gly Lys Gly Asn
130                 135                 140                 145
Met Asn Cys Ala Tyr Phe His Asn Gly Lys Met His Pro Thr Phe Cys
                150                 155                 160
Glu Asn Lys His Tyr Leu Met Cys Glu Arg Lys Ala Gly Met Thr Lys
            165                 170                 175
Val Asp Gln Leu Pro
        180
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<211> 92
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -24..-1
<400> 98
Met Thr Lys Leu Ala Gln Trp Leu Trp Gly Leu Ala Ile Leu Gly Ser
                -20                 -15                 -10
Thr Trp Val Ala Leu Thr Thr Gly Ala Leu Gly Leu Glu Leu Pro Leu
            -5                  1                   5
Ser Cys Gln Glu Val Leu Trp Pro Leu Pro Ala Tyr Leu Leu Val Ser
    10                  15                  20
Ala Gly Cys Tyr Ala Leu Gly Thr Val Gly Tyr Arg Val Ala Thr Phe
25                  30                  35                  40
His Asp Cys Glu Asp Ala Ala Arg Glu Leu Gln Ser Gln Ile Gln Glu
                45                  50                  55
Ala Arg Ala Asp Leu Ala Arg Arg Gly Leu Arg Phe
            60                  65
<210> 99
<211> 425
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -23..-1
<400> 99
Met Ala Ser Ser Ser Pro Asp Ser Pro Cys Ser Cys Asp Cys Phe Val
            -20                 -15                 -10
Ser Val Pro Pro Ala Ser Ala Ile Pro Ala Val Ile Phe Ala Lys Asn
        -5                  1                   5
Ser Asp Arg Pro Arg Asp Glu Val Gln Glu Val Val Phe Val Pro Ala
10                  15                  20                  25
Gly Thr His Thr Pro Gly Ser Arg Leu Gln Cys Thr Tyr Ile Glu Val
                30                  35                  40
Glu Gln Val Ser Lys Thr His Ala Val Ile Leu Ser Arg Pro Ser Trp
            45                  50                  55
Leu Trp Gly Ala Glu Met Gly Ala Asn Glu His Gly Val Cys Ile Gly
        60                  65                  70
Asn Glu Ala Val Trp Thr Lys Glu Pro Val Gly Glu Gly Glu Ala Leu
    75                  80                  85
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Leu Gly Met Asp Leu Leu Arg Leu Ala Leu Glu Arg Ser Ser Ser Ala
90                  95                  100                 105
Gln Glu Ala Leu His Val Ile Thr Gly Leu Leu Glu His Tyr Gly Gln
                110                 115                 120
Gly Gly Asn Cys Leu Glu Asp Ala Ala Pro Phe Ser Tyr His Ser Thr
            125                 130                 135
Phe Leu Leu Ala Asp Arg Thr Glu Ala Trp Val Leu Glu Thr Ala Gly
        140                 145                 150
Arg Leu Trp Ala Ala Gln Arg Ile Gln Glu Gly Ala Arg Asn Ile Ser
    155                 160                 165
Asn Gln Leu Ser Ile Gly Thr Asp Ile Ser Ala Gln His Pro Glu Leu
170                 175                 180                 185
Arg Thr His Ala Gln Ala Lys Gly Trp Trp Asp Gly Gln Gly Ala Phe
                190                 195                 200
Asp Phe Ala Gln Ile Phe Ser Leu Thr Gln Gln Pro Val Arg Met Glu
            205                 210                 215
Ala Ala Lys Ala Arg Phe Gln Ala Gly Arg Glu Leu Leu Arg Gln Arg
        220                 225                 230
Gln Gly Gly Ile Thr Ala Glu Val Met Met Gly Ile Leu Arg Asp Lys
    235                 240                 245
Glu Ser Gly Ile Cys Met Asp Ser Gly Gly Phe Arg Thr Thr Ala Ser
250                 255                 260                 265
Met Val Ser Val Leu Pro Gln Asp Pro Thr Gln Pro Cys Val His Phe
                270                 275                 280
Leu Thr Ala Thr Pro Asp Pro Ser Arg Ser Val Phe Lys Pro Phe Ile
            285                 290                 295
Phe Gly Val Gly Val Ala Gln Ala Pro Gln Val Leu Ser Pro Thr Phe
        300                 305                 310
Gly Ala Gln Asp Pro Val Arg Thr Leu Pro Arg Phe Gln Thr Gln Val
    315                 320                 325
Asp Arg Arg His Thr Leu Tyr Arg Gly His Gln Ala Ala Leu Gly Leu
330                 335                 340                 345
Met Glu Arg Asp Gln Asp Arg Gly Gln Gln Leu Gln Gln Lys Gln Gln
                350                 355                 360
Asp Leu Glu Gln Glu Gly Leu Glu Ala Thr Gln Gly Leu Leu Ala Gly
            365                 370                 375
Glu Trp Ala Pro Pro Leu Trp Glu Leu Gly Ser Leu Phe Gln Ala Phe
        380                 385                 390
Val Lys Arg Glu Ser Gln Ala Tyr Ala
    395                 400
<210> 100
<211> 87
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -62..-1
<400> 100
Met Ala Ile Phe Trp Ile Val His Ala His Phe Trp Ser Pro Leu Pro
        -60                 -55                 -50
Pro Arg Leu Pro His Gly Arg Cys Cys Cys Leu Lys Ala Pro Leu Pro
    -45                 -40                 -35
Pro Asp Val Gly Pro Leu Gln Val Ala Pro His Leu Phe Ser Val Pro
-30                 -25                 -20                 -15
Leu His Ile Leu Thr Val Pro Leu Leu Glu Pro Ala Arg Cys Ser Gly
                -10                 -5                  1
Ile Leu Val Phe Phe Leu His Gln Pro Val Ser Ser Leu Ser Phe Cys
        5                   10                  15
Tyr Phe Ile Gly Gly Trp Cys
    20                  25
<210> 101
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<211> 149
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -100..-1
<400> 101
Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn
-100 -95 -90 -85
Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr
-80 -75 -70
Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile
-65 -60 -55
Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp
-50 -45 -40
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn
-35 -30 -25
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met
-20 -15 -10 -5
Gly Gly Leu Gly Phe Ile Ile Leu Asp Arg Ser Asn Ala Pro Asn Ile
1 5 10
Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val
15 20 25
Leu Leu Ser Phe Phe Met Ala Arg Val Phe Met Arg Met Lys Leu Pro
30 35 40
Gly Tyr Leu Met Gly
45
<210> 102
<211> 187
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -35..-1
<400> 102
Met Ala Asn Asn Thr Thr Ser Leu Gly Ser Pro Trp Pro Glu Asn Phe
-35 -30 -25 -20
Trp Glu Asp Leu Ile Met Ser Phe Thr Val Ser Met Ala Ile Gly Leu
-15 -10 -5
Val Leu Gly Gly Phe Ile Trp Ala Val Phe Ile Cys Leu Ser Arg Arg
1 5 10
Arg Arg Ala Ser Ala Pro Ile Ser Gln Trp Ser Ser Ser Arg Arg Ser
15 20 25
Arg Ser Ser Tyr Thr His Gly Leu Asn Arg Thr Gly Phe Tyr Arg His
30 35 40 45
Ser Gly Cys Glu Arg Arg Ser Asn Leu Ser Leu Ala Ser Leu Thr Phe
50 55 60
Gln Arg Gln Ala Ser Leu Glu Gln Ala Asn Ser Phe Pro Arg Lys Ser
65 70 75
Ser Phe Arg Ala Ser Thr Phe His Pro Phe Leu Gln Cys Pro Pro Leu
80 85 90
Pro Val Glu Thr Glu Ser Gln Leu Val Thr Leu Pro Ser Ser Asn Ile
95 100 105
Ser Pro Thr Ile Ser Thr Ser His Ser Leu Ser Arg Pro Asp Tyr Trp
110 115 120 125
Ser Ser Asn Ser Leu Arg Val Gly Leu Ser Thr Pro Pro Pro Pro Ala
130 135 140
Tyr Glu Ser Ile Ile Lys Ala Phe Pro Asp Ser
145 150
<210> 103
<211> 123

<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -26..-1
<400> 103
Met Ala Thr Ala Ala Gly Ala Thr Tyr Phe Gln Arg Gly Ser Leu Phe
-25 -20 -15
Trp Phe Thr Val Ile Thr Leu Ser Phe Gly Tyr Tyr Thr Trp Val Val
-10 -5 1 5
Phe Trp Pro Gln Ser Ile Pro Tyr Gln Asn Leu Gly Pro Leu Gly Pro
10 15 20
Phe Thr Gln Tyr Leu Val Asp His His His Thr Leu Leu Cys Asn Gly
25 30 35
Tyr Trp Leu Ala Trp Leu Ile His Val Gly Glu Ser Leu Tyr Ala Ile
40 45 50
Val Leu Cys Lys His Lys Gly Ile Thr Ser Gly Arg Ala Gln Leu Leu
55 60 65 70
Trp Phe Leu Gln Thr Phe Phe Phe Gly Ile Ala Ser Leu Thr Ile Leu
75 80 85
Ile Ala Tyr Lys Arg Lys Arg Gln Lys Gln Thr
90 95
<210> 104
<211> 153
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -102..-1
<400> 104
Met Ala Ala Gly Leu Phe Gly Leu Ser Ala Arg Arg Leu Leu Ala Ala
-100 -95 -90
Ala Ala Thr Arg Gly Leu Pro Ala Ala Arg Val Arg Trp Glu Ser Ser
-85 -80 -75
Phe Ser Arg Thr Val Val Ala Pro Ser Ala Val Ala Gly Lys Arg Pro
-70 -65 -60 -55
Pro Glu Pro Thr Thr Pro Trp Gln Glu Asp Pro Glu Pro Glu Asp Glu
-50 -45 -40
Asn Leu Tyr Glu Lys Asn Pro Asp Ser His Gly Tyr Asp Lys Asp Pro
-35 -30 -25
Val Leu Asp Val Trp Asn Met Arg Leu Val Phe Phe Phe Gly Val Ser
-20 -15 -10
Ile Ile Leu Val Leu Gly Ser Thr Phe Val Ala Tyr Leu Pro Asp Tyr
-5 1 5 10
Arg Met Lys Glu Trp Ser Arg Arg Glu Ala Glu Arg Leu Val Lys Tyr
15 20 25
Arg Glu Ala Asn Gly Leu Pro Ile Met Glu Ser Asn Cys Phe Asp Pro
30 35 40
Ser Lys Ile Gln Leu Pro Glu Asp Glu
45 50
<210> 105
<211> 72
<212> PRT
<213> Homo sapiens
<400> 105
Leu Pro Val Ser Thr Arg Ile Ile Asn His Ile Tyr Ser Phe Pro Ser
1 5 10 15
Val Asp Leu Trp Ile Val Cys Ile Phe Thr Val Ser Val Ser His Leu
20 25 30
Phe Glu Lys Gly Thr Leu Tyr Gly Tyr Phe Tyr Val Ile Asn Ser Ser
35 40 45

```
Ile Asn Leu Cys Val Asn Asp Cys Leu Pro Val Met Asp Ser Ile Ser
    50                  55                  60
Leu Ser Pro Leu Phe Leu Ser His
65                  70
<210> 106
<211> 175
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -20..-1
<400> 106
Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser
-20                 -15                 -10                 -5
Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp
                1                   5                   10
Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp
        15                  20                  25
Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys
    30                  35                  40
Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu
45                  50                  55                  60
Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu
                65                  70                  75
Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu
            80                  85                  90
Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val Pro Arg Ile
        95                  100                 105
Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg
    110                 115                 120
Tyr Ser Asn Arg Leu Tyr Ala Tyr Glu Pro Ala Asp Thr Ala Leu Leu
125                 130                 135                 140
Leu Asp Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr Glu Leu
                145                 150                 155
<210> 107
<211> 303
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -20..-1
<400> 107
Met Ala Asp Ala Ala Ser Gln Val Leu Leu Gly Ser Gly Leu Thr Ile
-20                 -15                 -10                 -5
Leu Ser Gln Pro Leu Met Tyr Val Lys Val Leu Ile Gln Val Gly Tyr
                1                   5                   10
Glu Pro Leu Pro Pro Thr Ile Gly Arg Asn Ile Phe Gly Arg Gln Val
        15                  20                  25
Cys Gln Leu Pro Gly Leu Phe Ser Tyr Ala Gln His Ile Ala Ser Ile
    30                  35                  40
Asp Gly Arg Arg Gly Leu Phe Thr Gly Leu Thr Pro Arg Leu Cys Ser
45                  50                  55                  60
Gly Val Leu Gly Thr Val Val His Gly Lys Val Leu Gln His Tyr Gln
                65                  70                  75
Glu Ser Asp Lys Gly Glu Glu Leu Gly Pro Gly Asn Val Gln Lys Glu
            80                  85                  90
Val Ser Ser Ser Phe Asp His Val Ile Lys Glu Thr Thr Arg Glu Met
        95                  100                 105
Ile Ala Arg Ser Ala Ala Thr Leu Ile Thr His Pro Phe His Val Ile
    110                 115                 120
Thr Leu Arg Ser Met Val Gln Phe Ile Gly Arg Glu Ser Lys Tyr Cys
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125 130 135 140
Gly Leu Cys Asp Ser Ile Ile Thr Ile Tyr Arg Glu Glu Gly Ile Leu
145 150 155
Gly Phe Phe Ala Gly Leu Val Pro Arg Leu Leu Gly Asp Ile Leu Ser
160 165 170
Leu Trp Leu Cys Asn Ser Leu Ala Tyr Leu Val Asn Thr Tyr Ala Leu
175 180 185
Asp Ser Gly Val Ser Thr Met Asn Glu Met Lys Ser Tyr Ser Gln Ala
190 195 200
Val Thr Gly Phe Phe Ala Ser Met Leu Thr Tyr Pro Phe Val Leu Val
205 210 215 220
Ser Asn Leu Met Ala Val Asn Asn Cys Gly Leu Ala Gly Gly Cys Pro
225 230 235
Pro Tyr Ser Pro Ile Tyr Thr Ser Trp Ile Asp Cys Trp Cys Met Leu
240 245 250
Gln Lys Glu Gly Asn Met Ser Arg Gly Asn Ser Leu Phe Phe Arg Lys
255 260 265
Val Pro Phe Gly Lys Thr Tyr Cys Cys Asp Leu Lys Met Leu Ile
270 275 280

<210> 108
<211> 65
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -39..-1
<400> 108

Met Ser Thr Gly Ile Met Glu Tyr Lys Lys Thr Thr Lys Ala Met Lys
-35 -30 -25
Lys Lys Lys Asp Val Leu Phe Thr Ser Tyr Phe Lys Thr Ile Ala Phe
-20 -15 -10
Leu Leu Leu Tyr Val Ser Ala Gly Pro Ile Ser Arg Ile Phe Ile Arg
-5 1 5
Ser Leu Glu Leu Phe Leu Met Phe Pro Ser Asn Lys His Trp Tyr Ile
10 15 20 25
Ser

<210> 109
<211> 137
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -17..-1
<400> 109

Met Gly Phe Gly Ala Thr Leu Ala Val Gly Leu Thr Ile Phe Val Leu
-15 -10 -5
Ser Val Val Thr Ile Ile Ile Cys Phe Thr Cys Ser Cys Cys Cys Leu
1 5 10 15
Tyr Lys Thr Cys Arg Arg Pro Arg Pro Val Val Thr Thr Thr Thr Ser
20 25 30
Thr Thr Val Val His Ala Pro Tyr Pro Gln Pro Pro Ser Val Pro Pro
35 40 45
Ser Tyr Pro Gly Pro Ser Tyr Gln Gly Tyr His Thr Met Pro Pro Gln
50 55 60
Pro Gly Met Pro Ala Ala Pro Tyr Pro Met Gln Tyr Pro Pro Pro Tyr
65 70 75
Pro Ala Gln Pro Met Gly Pro Pro Ala Tyr His Glu Thr Leu Ala Gly
80 85 90 95
Gly Ala Ala Ala Pro Tyr Pro Ala Ser Gln Pro Pro Tyr Asn Pro Ala
100 105 110
Tyr Met Asp Ala Pro Lys Ala Ala Leu

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            115                 120
<210> 110
<211> 154
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -13..-1
<400> 110
Met Ala Leu Leu Leu Ser Val Leu Arg Val Leu Leu Gly Gly Phe Phe
            -10                 -5                  1
Ala Leu Val Gly Leu Ala Lys Leu Ser Glu Glu Ile Ser Ala Pro Val
    5                   10                  15
Ser Glu Arg Met Asn Ala Leu Phe Val Gln Phe Ala Glu Val Phe Pro
20                  25                  30                  35
Leu Lys Val Phe Gly Tyr Gln Pro Asp Pro Leu Asn Tyr Gln Ile Ala
                40                  45                  50
Val Gly Phe Leu Glu Leu Leu Ala Gly Leu Leu Leu Val Met Gly Pro
            55                  60                  65
Pro Met Leu Gln Glu Ile Ser Asn Leu Phe Leu Ile Leu Leu Met Met
        70                  75                  80
Gly Ala Ile Phe Thr Leu Ala Ala Leu Lys Glu Ser Leu Ser Thr Cys
    85                  90                  95
Ile Pro Ala Ile Val Cys Leu Gly Phe Leu Leu Leu Leu Asn Val Gly
100                 105                 110                 115
Gln Leu Leu Ala Gln Thr Lys Lys Val Val Arg Pro Thr Arg Lys Lys
                120                 125                 130
Thr Leu Ser Thr Phe Lys Glu Ser Trp Lys
            135                 140
<210> 111
<211> 103
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -36..-1
<400> 111
Met Ala Asn Leu Phe Ile Arg Lys Met Val Asn Pro Leu Leu Tyr Leu
    -35                 -30                 -25
Ser Arg His Thr Val Lys Pro Arg Ala Leu Ser Thr Phe Leu Phe Gly
-20                 -15                 -10                 -5
Ser Ile Arg Gly Ala Ala Pro Val Ala Val Glu Pro Gly Ala Ala Val
                1                   5                   10
Arg Ser Leu Leu Ser Pro Gly Leu Leu Pro His Leu Leu Pro Ala Leu
        15                  20                  25
Gly Phe Lys Asn Lys Thr Val Leu Asn Lys Arg Cys Lys Asp Cys Tyr
    30                  35                  40
Leu Val Lys Arg Arg Gly Arg Trp Tyr Val Tyr Cys Lys Thr His Pro
45                  50                  55                  60
Arg His Lys Gln Arg Gln Met
                65
<210> 112
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -74..-1
<400> 112
Met Pro Tyr Ala Phe Thr Ser Pro Cys Pro Cys Ser Phe Val Ser Leu
                -70                 -65                 -60
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Pro Glu Ile Ser Phe Tyr Phe Thr Lys Leu Leu Leu Ile Leu Lys Ala
            -55                 -50                 -45
Leu Pro Glu Ser Pro Phe Leu Leu Ala Ser Ser Pro Leu Pro Pro Leu
        -40                 -35                 -30
Pro Thr Thr Leu Arg Lys Phe Ile Pro Pro Pro Ser Leu Ile Ser Cys
    -25                 -20                 -15
Thr Cys Leu Leu Leu Tyr Leu Thr His Cys Ile Leu Gly Ile Cys Phe
-10                 -5                  1                   5
Ala Tyr Pro Phe Ile Leu
            10
<210> 113
<211> 395
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -310..-1
<400> 113
Met Asp Leu Gly Ile Pro Asp Leu Leu Asp Ala Trp Leu Glu Pro Pro
-310                 -305                 -300                 -295
Glu Asp Ile Phe Ser Thr Gly Ser Val Leu Glu Leu Gly Leu His Cys
                -290                 -285                 -280
Pro Pro Pro Glu Val Pro Val Thr Arg Leu Gln Glu Gln Gly Leu Gln
            -275                 -270                 -265
Gly Trp Lys Ser Gly Gly Asp Arg Gly Cys Gly Leu Gln Glu Ser Glu
        -260                 -255                 -250
Pro Glu Asp Phe Leu Lys Leu Phe Ile Asp Pro Asn Glu Val Tyr Cys
    -245                 -240                 -235
Ser Glu Ala Ser Pro Gly Ser Asp Ser Gly Ile Ser Glu Asp Ser Cys
-230                 -225                 -220                 -215
His Pro Asp Ser Pro Pro Ala Pro Arg Ala Thr Ser Ser Pro Met Leu
                -210                 -205                 -200
Tyr Glu Val Val Tyr Glu Ala Gly Ala Leu Glu Arg Met Gln Gly Glu
            -195                 -190                 -185
Thr Gly Pro Asn Val Gly Leu Ile Ser Ile Gln Leu Asp Gln Trp Ser
        -180                 -175                 -170
Pro Ala Phe Met Val Pro Asp Ser Cys Met Val Ser Glu Leu Pro Phe
    -165                 -160                 -155
Asp Ala His Ala His Ile Leu Pro Arg Ala Gly Thr Val Ala Pro Val
-150                 -145                 -140                 -135
Pro Cys Thr Thr Leu Leu Pro Cys Gln Thr Leu Phe Leu Thr Asp Glu
                -130                 -125                 -120
Glu Lys Arg Leu Leu Gly Gln Glu Gly Val Ser Leu Pro Ser His Leu
            -115                 -110                 -105
Pro Leu Thr Lys Ala Glu Glu Arg Val Leu Lys Lys Val Arg Arg Lys
        -100                 -95                  -90
Ile Arg Asn Lys Gln Ser Ala Gln Asp Ser Arg Arg Arg Lys Lys Glu
    -85                  -80                  -75
Tyr Ile Asp Gly Leu Glu Ser Arg Val Ala Ala Cys Ser Ala Gln Asn
-70                  -65                  -60                  -55
Gln Glu Leu Gln Lys Lys Val Gln Glu Leu Glu Arg His Asn Ile Ser
                -50                  -45                  -40
Leu Val Ala Gln Leu Arg Gln Leu Gln Thr Leu Ile Ala Gln Thr Ser
            -35                  -30                  -25
Asn Lys Ala Ala Gln Thr Ser Thr Cys Val Leu Ile Leu Leu Phe Ser
        -20                  -15                  -10
Leu Ala Leu Ile Ile Leu Pro Ser Phe Ser Pro Phe Gln Ser Arg Pro
    -5                   1                   5                   10
Glu Ala Gly Ser Glu Asp Tyr Gln Pro His Gly Val Thr Ser Arg Asn
                15                  20                  25
Ile Leu Thr His Lys Asp Val Thr Glu Asn Leu Glu Thr Gln Val Val
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            30                  35                  40
Glu Ser Arg Leu Arg Glu Pro Pro Gly Ala Lys Asp Ala Asn Gly Ser
        45                  50                  55
Thr Arg Thr Leu Leu Glu Lys Met Gly Gly Lys Pro Arg Pro Ser Gly
    60                  65                  70
Arg Ile Arg Ser Val Leu His Ala Asp Glu Met
75                  80                  85
<210> 114
<211> 93
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -18..-1
<400> 114
Met Ile His Leu Gly His Ile Leu Phe Leu Leu Leu Leu Pro Val Ala
            -15                 -10                 -5
Ala Ala Gln Thr Thr Pro Gly Glu Arg Ser Ser Leu Pro Ala Phe Tyr
        1                   5                   10
Pro Gly Thr Ser Gly Ser Cys Ser Gly Cys Gly Ser Leu Ser Leu Pro
15                  20                  25                  30
Leu Leu Ala Gly Leu Val Ala Ala Asp Ala Val Ala Ser Leu Leu Ile
                35                  40                  45
Val Gly Ala Val Phe Leu Cys Ala Arg Pro Arg Arg Ser Pro Ala Gln
            50                  55                  60
Glu Tyr Gly Lys Val Tyr Ile Asn Met Pro Gly Arg Gly
        65                  70                  75
<210> 115
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -21..-1
<400> 115
Met Arg Glu Met Pro Val Pro Ser Leu Ile Asn Leu Ala Ala Ser Arg
    -20                 -15                 -10
Thr Leu Ser Phe Cys Ile Ser Asp Asn His Val Ser Ser Pro Gly Pro
-5                  1                   5                   10
Ala Asn Pro Ser Cys Gly Leu His Pro His Trp Leu Arg Pro Leu Lys
            15                  20                  25
Leu Leu Thr Tyr Thr Cys Arg Glu Leu Lys Leu Gln Gly
        30                  35                  40
<210> 116
<211> 331
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -31..-1
<400> 116
Met Trp Leu Trp Glu Asp Gln Gly Gly Leu Leu Gly Pro Phe Ser Phe
    -30                 -25                 -20
Leu Leu Leu Val Leu Leu Leu Val Thr Arg Ser Pro Val Asn Ala Cys
-15                 -10                 -5                  1
Leu Leu Thr Gly Ser Leu Phe Val Leu Leu Arg Val Phe Ser Phe Glu
            5                   10                  15
Pro Val Pro Ser Cys Arg Ala Leu Gln Val Leu Lys Pro Arg Asp Arg
        20                  25                  30
Ile Ser Ala Ile Ala His Arg Gly Gly Ser His Asp Ala Pro Glu Asn
    35                  40                  45
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Thr Leu Ala Ala Ile Arg Gln Ala Ala Lys Asn Gly Ala Thr Gly Val
50                  55                  60                  65
Glu Leu Asp Ile Glu Phe Thr Ser Asp Gly Ile Pro Val Leu Met His
                70                  75                  80
Asp Asn Thr Val Asp Arg Thr Thr Asp Gly Thr Gly Arg Leu Cys Asp
            85                  90                  95
Leu Thr Phe Glu Gln Ile Arg Lys Leu Asn Pro Ala Ala Asn His Arg
        100                 105                 110
Leu Arg Asn Asp Phe Pro Asp Glu Lys Ile Pro Thr Leu Met Glu Ala
    115                 120                 125
Val Ala Glu Cys Leu Asn His Asn Leu Thr Ile Phe Phe Asp Val Lys
130                 135                 140                 145
Gly His Ala His Lys Ala Thr Glu Ala Leu Lys Lys Met Tyr Met Glu
                150                 155                 160
Phe Pro Gln Leu Tyr Asn Asn Ser Val Val Cys Ser Phe Leu Pro Glu
            165                 170                 175
Val Ile Tyr Lys Met Arg Gln Thr Asp Arg Asp Val Ile Thr Ala Leu
        180                 185                 190
Thr His Arg Pro Trp Ser Leu Ser His Thr Gly Asp Gly Lys Pro Arg
    195                 200                 205
Tyr Asp Thr Phe Trp Lys His Phe Ile Phe Val Met Met Asp Ile Leu
210                 215                 220                 225
Leu Asp Trp Ser Met His Asn Ile Leu Trp Tyr Leu Cys Gly Ile Ser
                230                 235                 240
Ala Phe Leu Met Gln Lys Asp Phe Val Ser Pro Ala Tyr Leu Lys Lys
            245                 250                 255
Trp Ser Ala Lys Gly Ile Gln Val Val Gly Trp Thr Val Asn Thr Phe
        260                 265                 270
Asp Glu Lys Ser Tyr Tyr Glu Ser His Leu Gly Ser Ser Tyr Ile Thr
    275                 280                 285
Asp Ser Met Val Glu Asp Cys Glu Pro His Phe
290                 295                 300
<210> 117
<211> 210
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -99..-1
<400> 117
Met Ala Ala Ser Val Glu Gln Arg Glu Gly Thr Ile Gln Val Gln Gly
                -95                 -90                 -85
Gln Ala Leu Phe Phe Arg Glu Ala Leu Pro Gly Ser Gly Gln Ala Arg
            -80                 -75                 -70
Phe Ser Val Leu Leu Leu His Gly Ile Arg Phe Ser Ser Glu Thr Trp
        -65                 -60                 -55
Gln Asn Leu Gly Thr Leu His Arg Leu Ala Gln Ala Gly Tyr Arg Ala
    -50                 -45                 -40
Val Ala Ile Asp Leu Pro Gly Leu Gly His Ser Lys Glu Ala Ala Ala
-35                 -30                 -25                 -20
Pro Ala Pro Ile Gly Glu Leu Ala Pro Gly Ser Phe Leu Ala Ala Val
                -15                 -10                 -5
Val Asp Ala Leu Glu Leu Gly Pro Pro Val Val Ile Ser Pro Ser Leu
            1                   5                   10
Ser Gly Met Tyr Ser Leu Pro Phe Leu Thr Ala Pro Gly Ser Gln Leu
    15                  20                  25
Pro Gly Phe Val Pro Val Ala Pro Ile Cys Thr Asp Lys Ile Asn Ala
30                  35                  40                  45
Ala Asn Tyr Ala Ser Val Lys Thr Pro Ala Leu Ile Val Tyr Gly Asp
                50                  55                  60
Gln Asp Pro Met Gly Gln Thr Ser Phe Glu His Leu Lys Gln Leu Pro
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            65                  70                  75
Asn His Arg Val Leu Ile Met Lys Gly Ala Gly His Pro Cys Tyr Leu
        80                  85                  90
Asp Lys Pro Glu Glu Trp His Thr Gly Leu Leu Asp Phe Leu Gln Gly
    95                  100                 105
Leu Gln
110
<210> 118
<211> 79
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -67..-1
<400> 118
Met Glu Leu Glu Ala Met Ser Arg Tyr Thr Ser Pro Val Asn Pro Ala
        -65                 -60                 -55
Val Phe Pro His Leu Thr Val Val Leu Leu Ala Ile Gly Met Phe Phe
    -50                 -45                 -40
Thr Ala Trp Phe Phe Val Tyr Glu Val Thr Ser Thr Lys Tyr Thr Arg
-35                 -30                 -25                 -20
Asp Ile Tyr Lys Glu Leu Leu Ile Ser Leu Val Ala Ser Leu Phe Met
                -15                 -10                 -5
Gly Phe Gly Val Leu Phe Leu Leu Leu Trp Val Gly Ile Tyr Val
            1               5                   10
<210> 119
<211> 84
<212> PRT
<213> Homo sapiens
<400> 119
Met Ala Val Trp Pro Glu Val Ser Gln Asn Arg Leu Thr Arg Gly Leu
1               5                   10                  15
Leu Leu Pro Asn Tyr Gln Leu Arg Gly Ser Val Pro Lys Arg Glu Lys
            20                  25                  30
Arg Pro Lys Arg Lys His Gln His Leu Phe Thr Pro Ser Glu Arg His
        35                  40                  45
Ser Val Cys Leu Asp Cys Leu Leu Glu Ile Ser Leu Ser Gly Lys Gln
    50                  55                  60
Trp Arg Asn Val Ile Ser Phe Asn Cys Phe Cys Thr Thr Lys Thr Leu
65                  70                  75                  80
Phe Trp Val Asn
<210> 120
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -20..-1
<400> 120
Met Ala Ser Leu Gly His Ile Leu Val Phe Cys Val Gly Leu Leu Thr
-20                 -15                 -10                 -5
Met Ala Lys Ala Glu Ser Pro Lys Glu His Asp Pro Phe Thr Tyr Asp
                1               5                   10
Tyr Gln Ser Leu Gln Ile Gly Gly Leu Val Ile Ala Gly Ile Leu Phe
        15                  20                  25
Ile Leu Gly Ile Leu Ile Val Leu Ser Arg Arg Cys Arg Cys Lys Phe
    30                  35                  40
Asn Gln Gln Gln Arg Thr Gly Glu Pro Asp Glu Glu Glu Gly Thr Phe
45                  50                  55                  60
Arg Ser Ser Ile Arg Arg Leu Ser Thr Arg Arg Arg
                65                  70
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<210> 121
<211> 210
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -14..-1
<400> 121

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Met Leu Thr Leu Leu Gly Leu Ser Leu Ile Leu Ala Gly Leu Ile Val
                -10                 -5                  1
Gly Gly Ala Cys Ile Tyr Lys His Phe Met Pro Lys Ser Thr Ile Tyr
        5                   10                  15
Arg Gly Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu
    20                  25                  30
Arg Gly Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile
35                  40                  45                  50
Arg Glu Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe
                55                  60                  65
Ser Asp Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met
            70                  75                  80
Thr Ala Tyr Leu Asp Leu Leu Leu Gly Asn Cys Tyr Leu Met Pro Leu
        85                  90                  95
Asn Thr Ser Ile Val Met Pro Pro Glu Asn Leu Val Glu Leu Phe Gly
    100                 105                 110
Lys Leu Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu
115                 120                 125                 130
Asp Leu Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile
                135                 140                 145
Phe Ile Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg
            150                 155                 160
Arg Asp Leu Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp
        165                 170                 175
Lys Ile Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys
    180                 185                 190
Gln Glu
195
```

<210> 122
<211> 205
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -139..-1
<400> 122

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Met Ala Pro Thr Arg Lys Asp Lys Leu Leu Gln Phe Tyr Pro Ser Leu
                -135                -130                -125
Glu Asp Pro Ala Ser Ser Arg Tyr Gln Asn Phe Ser Lys Gly Ser Arg
            -120                -115                -110
His Gly Ser Glu Glu Ala Tyr Ile Asp Pro Ile Ala Met Glu Tyr Tyr
        -105                 -100                -95
Asn Trp Gly Arg Phe Ser Lys Pro Pro Glu Gly Glu Ala Lys Asp Lys
    -90                 -85                 -80
Ala Gly Gly Gly Gly Ser Gly Val Gly Ala Gln Gly Arg Ser His Thr
-75                  -70                 -65                 -60
Ser Arg Gln Glu Arg Arg Leu Gly Leu Gly Ser Asp Asp Asp Ala Asn
                -55                 -50                 -45
Ser Tyr Glu Asn Val Leu Ile Cys Lys Gln Lys Thr Thr Glu Thr Gly
            -40                 -35                 -30
Ala Gln Gln Glu Asp Val Gly Gly Leu Cys Arg Gly Asp Leu Ser Leu
        -25                 -20                 -15
Ser Leu Ala Leu Lys Thr Gly Pro Thr Ser Gly Leu Cys Pro Ser Ala
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    -10                 -5                  1                   5
Ser Pro Glu Glu Asp Gly Glu Ser Glu Asp Tyr Gln Asn Ser Ala Ser
                10                  15                  20
Ile His Gln Trp Arg Glu Ser Arg Lys Val Met Gly Gln Leu Gln Arg
            25                  30                  35
Glu Ala Ser Pro Gly Pro Val Gly Ser Pro Asp Glu Glu Asp Gly Glu
        40                  45                  50
Pro Asp Tyr Val Asn Gly Glu Val Ala Ala Thr Glu Ala
    55                  60                  65
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<213> Homo sapiens
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<400> 123
Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
        -15                 -10                 -5
Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser
    1               5                   10                  15
Asp Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr
                20                  25                  30
Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe
            35                  40                  45
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
        50                  55                  60
Leu Pro Ser Glu Lys
    65
<210> 124
<211> 115
<212> PRT
<213> Homo sapiens
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<222> -51..-1
<400> 124
Met Gln Ala Gln Ala Pro Val Val Val Val Thr Gln Pro Gly Val Gly
    -50                 -45                 -40
Pro Gly Pro Ala Pro Gln Asn Ser Asn Trp Gln Thr Gly Met Cys Asp
-35                 -30                 -25                 -20
Cys Phe Ser Asp Cys Gly Val Cys Leu Cys Gly Thr Phe Cys Phe Pro
                -15                 -10                 -5
Cys Leu Gly Cys Gln Val Ala Ala Asp Met Asn Glu Cys Cys Leu Cys
            1                   5                   10
Gly Thr Ser Val Ala Met Arg Thr Leu Tyr Arg Thr Arg Tyr Gly Ile
    15                  20                  25
Pro Gly Pro Ile Cys Asp Asp Tyr Met Ala Thr Leu Cys Cys Pro His
30                  35                  40                  45
Cys Thr Leu Cys Gln Ile Lys Arg Asp Ile Asn Arg Arg Arg Ala Met
                50                  55                  60
Arg Thr Phe
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<211> 81
<212> PRT
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<222> -31..-1
<400> 125
Met Ser Asn Thr His Thr Val Leu Val Ser Leu Pro His Pro His Pro
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-30 -25 -20
Ala Leu Thr Cys Cys His Leu Gly Leu Pro His Pro Val Arg Ala Pro
-15 -10 -5 1
Arg Pro Leu Pro Arg Val Glu Pro Trp Asp Pro Arg Trp Gln Asp Ser
5 10 15
Glu Leu Arg Tyr Pro Gln Ala Met Asn Ser Phe Leu Asn Glu Arg Ser
20 25 30
Ser Pro Cys Arg Thr Leu Arg Gln Glu Ala Ser Ala Asp Arg Cys Asp
35 40 45
Leu
50

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<211> 235
<212> PRT
<213> Homo sapiens
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<400> 126

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-35 -30 -25
Thr His Ile Asp Val His Ile His Gln Glu Ser Ala Leu Ala Lys Leu
-20 -15 -10
Leu Leu Thr Cys Cys Ser Ala Leu Arg Pro Arg Ala Thr Gln Ala Arg
-5 1 5
Gly Ser Ser Arg Leu Leu Val Ala Ser Trp Val Met Gln Ile Val Leu
10 15 20 25
Gly Ile Leu Ser Ala Val Leu Gly Gly Phe Phe Tyr Ile Arg Asp Tyr
30 35 40
Thr Leu Leu Val Thr Ser Gly Ala Ala Ile Trp Thr Gly Ala Val Ala
45 50 55
Val Leu Ala Gly Ala Ala Ala Phe Ile Tyr Glu Lys Arg Gly Gly Thr
60 65 70
Tyr Trp Ala Leu Leu Arg Thr Leu Leu Ala Leu Ala Ala Phe Ser Thr
75 80 85
Ala Ile Ala Ala Leu Lys Leu Trp Asn Glu Asp Phe Arg Tyr Gly Tyr
90 95 100 105
Ser Tyr Tyr Asn Ser Ala Cys Arg Ile Ser Ser Ser Ser Asp Trp Asn
110 115 120
Thr Pro Ala Pro Thr Gln Ser Pro Glu Glu Val Arg Arg Leu His Leu
125 130 135
Cys Thr Ser Phe Met Asp Met Leu Lys Ala Leu Phe Arg Thr Leu Gln
140 145 150
Ala Met Leu Leu Gly Val Trp Ile Leu Leu Leu Leu Ala Ser Leu Ala
155 160 165
Pro Leu Trp Leu Tyr Cys Trp Arg Met Phe Pro Thr Lys Gly Lys Arg
170 175 180 185
Asp Gln Lys Glu Met Leu Glu Val Ser Gly Ile
190 195

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<211> 62
<212> PRT
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Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys Leu Ile Phe Gly Leu
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Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser Leu Gln Ile Asp Val
-5 1 5 10

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Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr Gly Val Arg Gln Val
            15                  20                  25
Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu Phe Gln Ala
        30                  35                  40
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<212> PRT
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Met Gly Leu Ser Ser Ser Glu Gly Asp Ile Pro
1               5                   10
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<211> 56
<212> PRT
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<222> -34..-1
<400> 129
Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr
                -30                 -25                 -20
Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val
            -15                 -10                 -5
Phe Gly Asp Pro Ala Ser Met Phe Cys Lys Val Phe Asp Leu Leu Val
        1               5                   10
Leu Asn Lys Ile Leu Leu Gly Leu
15                  20
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<211> 542
<212> DNA
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<222> 15..311
<223> sig_peptide
<222> 15..110
<223> Von Heijne matrix
      score 3.5
      seq RIHLCQRSXGSQG/VR
<223> polyA_signal
<222> 507..512
<223> polyA_site
<222> 531..542
<400> 130
agatattaac aagg atg gcg gcg gcc gca gca agt cga gga gtc ggg gca       50
               Met Ala Ala Ala Ala Ala Ser Arg Gly Val Gly Ala
                   -30                 -25
aag ctg ggc ctg cgt gag att cgc atc cac tta tgt cag cgc tcg scc       98
Lys Leu Gly Leu Arg Glu Ile Arg Ile His Leu Cys Gln Arg Ser Xaa
-20                 -15                 -10                 -5
ggc agc cag ggc gtc agg gac ttc att gag aaa cgc tac gtg gag ctg      146
Gly Ser Gln Gly Val Arg Asp Phe Ile Glu Lys Arg Tyr Val Glu Leu
                1               5                   10
aag aag gcg aat ccc gac cta ccc atc cta atc cgc gaa tgc tcc gat      194
Lys Lys Ala Asn Pro Asp Leu Pro Ile Leu Ile Arg Glu Cys Ser Asp
        15                  20                  25
gtg cag ccc aag ctc tgg gcc cgc tac gca ttt ggc caa rag acg aat      242
Val Gln Pro Lys Leu Trp Ala Arg Tyr Ala Phe Gly Gln Xaa Thr Asn
    30                  35                  40
gtc cct ttg aac aac ttc agt gct gat cag gta acc aga rcc ctg gag      290
Val Pro Leu Asn Asn Phe Ser Ala Asp Gln Val Thr Arg Xaa Leu Glu
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45                  50                  55                  60
aac gtt cta agt ggt aaa gcc tgaagcctcc actgaggatt aagagcaaca          341
Asn Val Leu Ser Gly Lys Ala
                65
gccccagagc ctgggctctg ctggacttar tataatgtga aaaaaatgtg ttctcctatt     401
cctcataaag cttgtgctgt aaaatacttt ctcagggtgt tcttgtcctc atctaccctc     461
taccccttac tgtgcaacca ctgaggcaaa gtagcttaat ataaaaataa aactttattc     521
tgtctcatca aaaaaaaaaa a                                            542
<210> 131
<211> 909
<212> DNA
<213> Homo sapiens
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<223> CDS
<222> 50..529
<223> sig_peptide
<222> 50..130
<223> Von Heijne matrix
      score 7.19999980926514
      seq VLWLSGLSEPGAA/RQ
<223> polyA_signal
<222> 877..882
<223> polyA_site
<222> 899..909
<400> 131
aagacggtgg cgcgattggg acagtcgcca gggatggctg agcgtgaag atg cag cgg      58
                                                    Met Gln Arg
                                                        -25
gtg tcc ggg ctg ctc tcc tgg acg ctg agc aga gtc ctg tgg ctc tcc       106
Val Ser Gly Leu Leu Ser Trp Thr Leu Ser Arg Val Leu Trp Leu Ser
            -20                 -15                 -10
ggc ctc tct gag ccg gga gct gcc cgg cag ccc cgg atc atg gaa gag       154
Gly Leu Ser Glu Pro Gly Ala Ala Arg Gln Pro Arg Ile Met Glu Glu
        -5                  1                   5
aaa gcg cta gag gtt tat gat ttg att aga act atc cgg gac cca gaa       202
Lys Ala Leu Glu Val Tyr Asp Leu Ile Arg Thr Ile Arg Asp Pro Glu
    10                  15                  20
aag ccc aat act tta gaa gaa ctg gaa gtg gtc tcg gaa agt tgt gtg       250
Lys Pro Asn Thr Leu Glu Glu Leu Glu Val Val Ser Glu Ser Cys Val
25                  30                  35                  40
gaa gtt cag gag ata aat gaa gaa raa tat ctg gtt att atc agg ttc       298
Glu Val Gln Glu Ile Asn Glu Glu Xaa Tyr Leu Val Ile Ile Arg Phe
                45                  50                  55
acg cca aca gta cct cat tgc tct ttg gcg act ctt att ggg ctg tgc       346
Thr Pro Thr Val Pro His Cys Ser Leu Ala Thr Leu Ile Gly Leu Cys
            60                  65                  70
yta arw kta aaa ctt cag cga tgt tta cca ttt aaa cat aag ttg gma       394
Leu Xaa Xaa Lys Leu Gln Arg Cys Leu Pro Phe Lys His Lys Leu Xaa
        75                  80                  85
atc tac att tct gaa gga acc cac tca rsa gar gaa gac atc aat wwk       442
Ile Tyr Ile Ser Glu Gly Thr His Ser Xaa Glu Glu Asp Ile Asn Xaa
    90                  95                  100
cag ata aat gac aaa gag cgw ktg gca kct gca atg gaa aac ccc awc       490
Gln Ile Asn Asp Lys Glu Arg Xaa Ala Xaa Ala Met Glu Asn Pro Xaa
105                 110                 115                 120
tta cgg gaa att gtg gaa cag tgt gtc ctt gaa cct gac tgawakctgt        539
Leu Arg Glu Ile Val Glu Gln Cys Val Leu Glu Pro Asp
                125                 130
tttaaragcc actggcctgt aattgtttga tatatttgtt taaactcttt gtataatgtc     599
agaggactca tgtttaatac ataggtgatt tgtacctcag agcatttttt aaaggattct     659
ttccaagcga gatttaatta taaggtagta cctaatttgt tcaatgtata acattctcag     719
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gatttgtaac acttaaatga tcagacagaa taatattttc tagttattat gtgtaagatg    779
agttgctatt tttctgatgc tcattctgat acaactattt ttcgtgtcaa atatctactg    839
tgcccaaatg tactcaattt aaatcattac tctgtaaaat aaataagcag atgattctta    899
aaaaaaaaaa                                                          909
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<223> CDS
<222> 240..416
<223> sig_peptide
<222> 240..305
<223> Von Heijne matrix
      score 3.70000004768372
      seq AVLDCAFYDPTHA/WS
<223> polyA_signal
<222> 1117..1122
<223> polyA_site
<222> 1139..1149
<400> 132
actagcctgc gagtgttctg agggaagcaa ggaggcggcg gcggccgcag cgagtggcga     60
gtagtggaaa cgttgcttct gaggggtgtc caagatgacc ggttctaacg gagttcaagc    120
tgaaccagcc acccgaggat ggcatctcct ccgtgaagtt cagccccaac acctcccagt    180
tcctgcttgt ctcctcctgg gacacgtccg tgcgtctcta cgatgtgccg gccaactcc     239
atg cgg ctc aag tac cag cac acc ggc gcc gtc ctg gac tgc gcc ttc      287
Met Arg Leu Lys Tyr Gln His Thr Gly Ala Val Leu Asp Cys Ala Phe
       -20                 -15                 -10
tac gat cca acg cat gcc tgg agt gga gga cta gat cat caa ttg aaa      335
Tyr Asp Pro Thr His Ala Trp Ser Gly Gly Leu Asp His Gln Leu Lys
    -5                  1               5                  10
atg cat gat ttg aac act gat caa gaa aat ctt gtt ggg acc atg atg      383
Met His Asp Leu Asn Thr Asp Gln Glu Asn Leu Val Gly Thr Met Met
               15                  20                  25
ccc cta tca gat gtg ttg aat act gtc cac aaa tgaatgtgat ggtcmctgga    436
Pro Leu Ser Asp Val Leu Asn Thr Val His Lys
           30                  35
akttgggatc aaacagttaa actgtgggat cccamaactc cttgtaatgc tgggaccttc    496
tctcmkcctg aaaaggtata taccctctca gtgtctggag accggctgat tgtgggaaca    556
gcaggccgca gagtgttggt gtgggactta cggaacatgg gttacgtgca gcagcgcagg    616
gagtccagcc tgaaatacca gactcgctgc atacgagcgt ttccaaacaa gcagggttat    676
gtattaagct ctattgaagg ccgagtggca gttgagtatt tggacccaag ccctgaggta    736
cagaagaaga agtatgcctt caaatgtcac agactaaaag aaaataatat tgagcagatt    796
tacccagtca atgccatttc ttttcacaat atccacaata catttgccac aggtggttct    856
gatggctttg taaatatttg ggatccattt aacaaaaagc gactgtgcca attccatcgg    916
taccccacga gcatcgcatc acttgccttc agtaatgatg ggactacgct tgcaatagcg    976
tcatcatata tgtatgaaat ggatgacaca gaacatcctg aagatggtat cttcattcgc   1036
caagtgacag atgcagaaac aaaacccaag tcaccatgta cttgacaaga tttcatttac   1096
ttaagtgcca tgttgatgat aataaaacaa ttcgtactcc ccaaaaaaaa aaa           1149
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<211> 921
<212> DNA
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<223> CDS
<222> 111..446
<223> sig_peptide
<222> 111..254
<223> Von Heijne matrix
      score 4.90000009536743
      seq PSLAAGLLFGSLA/GL
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<223> polyA_signal
<222> 890..895
<223> polyA_site
<222> 909..921
<400> 133
agacacctcg cagtcattcc tgcggcttgc gcgcccttgt agacagccgg ggccttcgtg 60
agaccggtgc aggcctgggg tagtctccag tctggacaga gaagagaaaa atg cag 116
Met Gln
gac act ggc tca gta gtg cct ttg cat tgg ttt ggc ttt ggc tac gca 164
Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly Tyr Ala
-45 -40 -35
gca ctg gtt gct tct ggt ggg atc att ggc tat gta aaa gca ggb agc 212
Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala Gly Ser
-30 -25 -20 -15
gtg ccg tcc ctg gct gca ggg ctg ctc ttt ggc agt cta gcc ggc ctg 260
Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala Gly Leu
-10 -5 1
ggt gct tac cag ctg tct cag gat cca agg aac gtt tgg gtt ttc cta 308
Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val Phe Leu
5 10 15
gct aca tct ggt acc ttg gct ggc att atg gga atg agg ttc tac cac 356
Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe Tyr His
20 25 30
tct gga aaa ttc atg cct gca ggt tta att gca ggt gcc akt ttg ctg 404
Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Xaa Leu Leu
35 40 45 50
atg gtc gcc aaa att gga gtt agt atg ttc aac aga ccc cat 446
Met Val Ala Lys Ile Gly Val Ser Met Phe Asn Arg Pro His
55 60
tagcagaakt catgttccag cttagactga tgaagaatta aaaatctgca tcttccacta 506
ttttcaatat attaagagaa ataagtgcag cattttgca tctgacattt tacctaaaaa 566
aaaagacacc aaacttggma raraggtgga aaatcagtca tgattacaaa cctacagagg 626
tggcgagtat gtaacacaag agcttaataa gaccctcata ragcttgatt cttgtawatt 686
gatgttgtct tttctttckg tatctgtagg taaatctcaa gggtaaaatg ttaggtgtca 746
gctttcaggg ctctgaaacc chattccctg ctctgaggaa cagtgtgaaa aaaagtcttt 806
taggagattt acaatatctg ttcttttgct catcttagac cacagactga ctttgaaatt 866
atgttaagtg aaatatcaat gaaaataaag tttactataa ataataaaaa aaaaa 921
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<211> 916
<212> DNA
<213> Homo sapiens
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<223> CDS
<222> 123..455
<223> sig_peptide
<222> 123..290
<223> Von Heijne matrix
score 4.5
seq FCAGVLLTLLLIA/FI
<223> polyA_signal
<222> 886..891
<223> polyA_site
<222> 904..916
<400> 134
aaagtaatct ttatttcgtc atttttgara catagaagcc gtaacggaag caagtgaaat 60
gctcagtctt agacgactgc gtcgtgctat gaccggactt tttcttgaaa ggggatgaca 120
gc atg gga ggc aat ggc tcc aca tgt aaa ccc gac act gaa aga caa 167
Met Gly Gly Asn Gly Ser Thr Cys Lys Pro Asp Thr Glu Arg Gln
-55 -50 -45
ggc act ctc tcc aca gca gcc cca aca act agc cct gca ccc tgt ctc 215
Gly Thr Leu Ser Thr Ala Ala Pro Thr Thr Ser Pro Ala Pro Cys Leu

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    -40                 -35                 -30
tct aac cac cac aac aaa aaa cat tta atc ctt gcc ttt tgt gct ggg      263
Ser Asn His His Asn Lys Lys His Leu Ile Leu Ala Phe Cys Ala Gly
-25                 -20                 -15                 -10
gtt cta ctg aca ctg ctg ctg ata gcc ttt atc ttc ctc atc ata aag      311
Val Leu Leu Thr Leu Leu Leu Ile Ala Phe Ile Phe Leu Ile Ile Lys
                -5                  1                   5
agc tac aga aaa tat cac tcc aag ccc cag gcc cca gat cct cac tca      359
Ser Tyr Arg Lys Tyr His Ser Lys Pro Gln Ala Pro Asp Pro His Ser
        10                  15                  20
gat cct cca kcc rrg ctt tca tcc atc cca ggg gaa tca ctt acc tat      407
Asp Pro Pro Xaa Xaa Leu Ser Ser Ile Pro Gly Glu Ser Leu Thr Tyr
    25                  30                  35
gcc agc aca ags ktt caa act ctc aga aka ama gag cam yca ctt ggc      455
Ala Ser Thr Xaa Xaa Gln Thr Leu Arg Xaa Xaa Glu Xaa Xaa Leu Gly
40                  45                  50                  55
tgagaaccat tctgcagact ttgaccccak kgtctatgct caaattaaag taacaaacta    515
actcagcttt tccaatgagg cttgaatcca tttcctcksa tctcagccct atcttcacas    575
atcactttca ctttttttaca wattttggac caccacctgt gtgaaactgc agtcggagtt    635
gtttasatgt gatctggcaa tgctatccag catctttgga gaccaatggt cagtcttttc    695
ctggccakag gaaasattga tggccctccc asttggaact gacagcctgt gagccccttg    755
ggggcataga ctgccttcct tggacccttc caaagtgtgt ggtacrgagc tcagtgcaca    815
gagtattcac ccagcatcat gaatcaactt gggaggagtc aaccaaatga acaatctacc    875
aaaaatttca aataaagtca aacccccccac aaaaaaaaaa a                       916
<210> 135
<211> 520
<212> DNA
<213> Homo sapiens
<220>
<223> CDS
<222> 2..433
<223> sig_peptide
<222> 2..232
<223> Von Heijne matrix
      score 4.40000009536743
      seq FEARIALLPLLQA/ET
<223> polyA_signal
<222> 488..493
<223> polyA_site
<222> 510..520
<400> 135
a atg gcg gcg tca aag gtg aag cag gac atg cct ccr mcg ggg ggc tat      49
  Met Ala Ala Ser Lys Val Lys Gln Asp Met Pro Pro Xaa Gly Gly Tyr
        -75                 -70                 -65
ggg ccc atc gac tac aaa cgg aac ttg ccg cgt cga gga ctg tcg ggc       97
Gly Pro Ile Asp Tyr Lys Arg Asn Leu Pro Arg Arg Gly Leu Ser Gly
    -60                 -55                 -50
tac agc atg ctg gcc ata ggg att gga acc ctg atc tac ggg cac tgg      145
Tyr Ser Met Leu Ala Ile Gly Ile Gly Thr Leu Ile Tyr Gly His Trp
-45                 -40                 -35                 -30
agc ata atg aag tgg aac cgt gag cgc agg cgc cta caa atc gag gac      193
Ser Ile Met Lys Trp Asn Arg Glu Arg Arg Arg Leu Gln Ile Glu Asp
                -25                 -20                 -15
ttc gag gct cgc atc gcg ctg ttg cca ctg tta cag gca gaa acc gac      241
Phe Glu Ala Arg Ile Ala Leu Leu Pro Leu Leu Gln Ala Glu Thr Asp
            -10                 -5                  1
cgg agg acc ttg cag atg ctt cgg gag aac ctg gag gag gag gcc atc      289
Arg Arg Thr Leu Gln Met Leu Arg Glu Asn Leu Glu Glu Glu Ala Ile
    5                   10                  15
atc atg aag gac gtg ccc gac tgg aag gtg ggg gak tct gtg tyc cac      337
Ile Met Lys Asp Val Pro Asp Trp Lys Val Gly Xaa Ser Val Xaa His
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20                  25                  30                  35
aca acc cgc tgg gtg ccc ccc ttg atc ggg gag ctg tac ggg ctg cgc      385
Thr Thr Arg Trp Val Pro Pro Leu Ile Gly Glu Leu Tyr Gly Leu Arg
                40                  45                  50
acc aca aag gag gct ctc cat gcc agc cac ggc ttc atg tgg tac acg      433
Thr Thr Lys Glu Ala Leu His Ala Ser His Gly Phe Met Trp Tyr Thr
            55                  60                  65
taggccctgt gccctccggc cacctggatc cctgcccctc cccactgggg acggaataaa    493
tgctctgcag acctggaaaa aaaaaaa                                        520
<210> 136
<211> 568
<212> DNA
<213> Homo sapiens
<220>
<223> CDS
<222> 34..363
<223> sig_peptide
<222> 34..87
<223> Von Heijne matrix
      score 8.30000019073486
      seq LLSLSSLPLVLLG/WE
<223> polyA_signal
<222> 536..541
<223> polyA_site
<222> 558..568
<400> 136
aaccagactt ctgacccctt gggcaacagc cag atg gag act ggt cgc ctt ttg      54
                                    Met Glu Thr Gly Arg Leu Leu
                                                -15
agc ctc agc tct ctt cct ctt gtt ctc cta ggg tgg gag tac agc agc      102
Ser Leu Ser Ser Leu Pro Leu Val Leu Leu Gly Trp Glu Tyr Ser Ser
    -10                 -5                  1                   5
caa acg ctg aac tta gtc cca tcc act tcc atc tta tcc ttt gtg ccc      150
Gln Thr Leu Asn Leu Val Pro Ser Thr Ser Ile Leu Ser Phe Val Pro
                10                  15                  20
ttc atc ccc ctg cat ctt gtc ctt ttt gcc ctc tgg tac ctc cca gtg      198
Phe Ile Pro Leu His Leu Val Leu Phe Ala Leu Trp Tyr Leu Pro Val
            25                  30                  35
ccc cat cat ctc tac ccc cag gga ctc gga rat cat gca gca raa gca      246
Pro His His Leu Tyr Pro Gln Gly Leu Gly Xaa His Ala Ala Xaa Ala
        40                  45                  50
gaa raa ggc aaa cga raa gaa gga gga acc caa kta gct ttg tgg ctt      294
Glu Xaa Gly Lys Arg Xaa Glu Gly Gly Thr Gln Xaa Ala Leu Trp Leu
    55                  60                  65
cgt gtc caa ccc tct tgc cct tcg cct gtg tgc ctg gag cca gtc cca      342
Arg Val Gln Pro Ser Cys Pro Ser Pro Val Cys Leu Glu Pro Val Pro
70                  75                  80                  85
cca cgc tcg cgt ttc ctc ctg tagtgctcac aggtcccagc accgatggca        393
Pro Arg Ser Arg Phe Leu Leu
                90
ttccctttgc cctgagtctg carcgggtcc cttttgtgct tccttcccct caggtagcct    453
ctctcccccc gggccactcc cgggggtgag ggggtttacc ccttcccagt gtttttatt     513
cctgtggggc tcaccccaaa gtattaaaag tagctttgta attcaaaaaa aaaaa         568
<210> 137
<211> 419
<212> DNA
<213> Homo sapiens
<220>
<223> CDS
<222> 50..286
<223> sig_peptide
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<222> 50..157
<223> Von Heijne matrix
      score 4.80000019073486
      seq VLLAIGMFFTAWF/FV
<223> polyA_signal
<222> 385..390
<223> polyA_site
<222> 405..416
<400> 137
agacgtgttc ttccggtggc ggasggcgga ttagccttcg cggggcaaa atg gag ctc      58
                                                    Met Glu Leu
                                                      -35
gag gcc atg agc aga tat acc agc cca gtg aac cca gct gtc ttc ccc      106
Glu Ala Met Ser Arg Tyr Thr Ser Pro Val Asn Pro Ala Val Phe Pro
          -30                 -25                 -20
cat ctg acc gtg gtg ctt ttg gcc att ggc atg ttc ttc acc gcc tgg      154
His Leu Thr Val Val Leu Leu Ala Ile Gly Met Phe Phe Thr Ala Trp
       -15                 -10                 -5
ttc ttc gtt tac gag gtc acc tct acc aag tac act cgt gat atc tat      202
Phe Phe Val Tyr Glu Val Thr Ser Thr Lys Tyr Thr Arg Asp Ile Tyr
    1               5                  10                  15
aaa gag ctc ctc atc tcc tta gtg gcc tca ctc ttc atg ggc ttt gga      250
Lys Glu Leu Leu Ile Ser Leu Val Ala Ser Leu Phe Met Gly Phe Gly
                20                  25                  30
gtc ctc ttc ctg ctg ctc tgg gtt ggc atc tac gtg tgagcaccca           296
Val Leu Phe Leu Leu Leu Trp Val Gly Ile Tyr Val
            35                  40
agggtaacaa ccagatggct tcactgaaac ctgcttttgt aaattacttt tttttactgt    356
tgctggaagt gtcccacctg ctgctcataa taaatgcaga agtatagcaa aaaaaaaaaa    416
ccc                                                                 419
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<223> Von Heijne matrix
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      seq LGAAALALLLANT/DV
<223> polyA_site
<222> 1277..1289
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aatatacttc tttgtcaaga gaagcagagg tgtggacgct gtgtatgaa atg tct ttc      58
                                                    Met Ser Phe
ctc cag gac cca agt ttc ttc acc atg ggg atg tgg tcc att ggt gca      106
Leu Gln Asp Pro Ser Phe Phe Thr Met Gly Met Trp Ser Ile Gly Ala
    -30                 -25                 -20
gga gcc ctg ggg gct gct gcc ttg gca ttg ctg ctt gcc aac aca gac      154
Gly Ala Leu Gly Ala Ala Ala Leu Ala Leu Leu Leu Ala Asn Thr Asp
-15                 -10                 -5                  1
gtg ttt ctg tcc aag ccc cag aaa gcg gcc ctg gag tac ctg gag gat      202
Val Phe Leu Ser Lys Pro Gln Lys Ala Ala Leu Glu Tyr Leu Glu Asp
            5                  10                  15
ata gac ctg aaa aca ctg gag aag gaa cca agg act ttc aaa gca aag      250
Ile Asp Leu Lys Thr Leu Glu Lys Glu Pro Arg Thr Phe Lys Ala Lys
        20                  25                  30
gag cta tgg gaa aaa aat gga gct gtg att atg gcc gtg cgg agg cca      298
Glu Leu Trp Glu Lys Asn Gly Ala Val Ile Met Ala Val Arg Arg Pro
```

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     35                  40                  45
ggc tgt ttc ctc tgt cga gag gaa gct gcg gat ctg tcc tcc ctg aaa      346
Gly Cys Phe Leu Cys Arg Glu Glu Ala Ala Asp Leu Ser Ser Leu Lys
50                  55                  60                  65
agc atg ttg gac cag ctg ggc gtc ccc ctc tat gca gtg gta aag gas      394
Ser Met Leu Asp Gln Leu Gly Val Pro Leu Tyr Ala Val Val Lys Xaa
                70                  75                  80
cac atc rgg act gaa ktg aag gat ttc cag cct tat ttc aaa gga gaa      442
His Ile Xaa Thr Glu Xaa Lys Asp Phe Gln Pro Tyr Phe Lys Gly Glu
            85                  90                  95
atc ttc ctg gat gaa aar aaa aag ttc tat ggt cca caa agg cgg aag      490
Ile Phe Leu Asp Glu Lys Lys Lys Phe Tyr Gly Pro Gln Arg Arg Lys
        100                 105                 110
atg atg ttt atg gga ttt atc cgt ctg gga atg tgg tac aac ttc ttc      538
Met Met Phe Met Gly Phe Ile Arg Leu Gly Met Trp Tyr Asn Phe Phe
    115                 120                 125
cga rcc tgg aac gga rgc ttc tct gga aac ctg gaa gga raa ggc ttc      586
Arg Xaa Trp Asn Gly Xaa Phe Ser Gly Asn Leu Glu Gly Xaa Gly Phe
130                 135                 140                 145
atc ctt ggg gga att ttc gtg gtg gga tca asg aaa gca ggg cat tct      634
Ile Leu Gly Gly Ile Phe Val Val Gly Ser Xaa Lys Ala Gly His Ser
                150                 155                 160
tct tgarcmccga gaaaaagaat ttggagacaa agtaaaccta ctttctgttc           687
Ser
tggaagctgc taagatgatc aaaccacaga ctttggcctc agagaaaaaa tgattgtgtg    747
aaactgccca gctcagggat aaccagggac attcacctgt gttcatggga tgtattgttt    807
ccactcgtgt ccctaaggag tgagaaaccc atttatactc tactctcagt atggattatt    867
aatgtatttt aatattctgt ttaggcccac taaggcaaaa tasccccaaa acaagactga    927
caaaaatctg aaaaactaat gaggattatt aagctaaaac ctgggaaata ggaggcttaa    987
aattgactgc caggctgggt gcagtggctc acacctgtaa tcccagcact ttgggaggcc   1047
aaggtgagca agtcacttga ggtcgggagt tcgagaccag cctgagcaac atggcgaaac   1107
cccgtctcta ckaaaaatac araaatcacc cgggtgtggt ggcaggcacc tgtagtccca   1167
gctacccggg aggctgaggc aggagaatca cttgaacctg ggaggtggag gttgcggtga   1227
gctgagatca caccactgta ttccagcctg ggtgactgag actctaacca aaaaaaaaaa   1287
aa                                                                  1289
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<223> Von Heijne matrix
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      seq LTPLFFMFPTGFS/SP
<223> polyA_site
<222> 704..715
<400> 139
acttcccttc cccctctagc attgctacct tctctcctac acgcacgcag gcatataaac     60
gtaggttttt g atg ctc ctc tgc ctg ttg acc ccg cta ttt ttc atg ttt     110
             Met Leu Leu Cys Leu Leu Thr Pro Leu Phe Phe Met Phe
                        -15                 -10
cca aca ggt ttt tct tcc ccc agt ccc tca gct gct gct gct gct cag      158
Pro Thr Gly Phe Ser Ser Pro Ser Pro Ser Ala Ala Ala Ala Ala Gln
-5                  1               5                   10
gag gtc aga tct gcc act gat ggt aat acc agc acc act ccg ccc acc      206
Glu Val Arg Ser Ala Thr Asp Gly Asn Thr Ser Thr Thr Pro Pro Thr
            15                  20                  25
tct gcc aar aar aka aag tta aac agc agc agc agt agc agc agt aac      254
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Ser Ala Lys Lys Xaa Lys Leu Asn Ser Ser Ser Ser Ser Ser Ser Asn
        30                  35                  40
agt agt aac gag aga gaa gac ttt gat tcs acc tct tcc tcc tct tcc      302
Ser Ser Asn Glu Arg Glu Asp Phe Asp Ser Thr Ser Ser Ser Ser Ser
    45                  50                  55
act cct cct tta caa ccc agg gat tcg gca tcc cct tca acc tcg tcc      350
Thr Pro Pro Leu Gln Pro Arg Asp Ser Ala Ser Pro Ser Thr Ser Ser
60                  65                  70                  75
ttc tgc ctg ggg gtt tca gtg gct gct tcc agc cac gta ccg ata swg      398
Phe Cys Leu Gly Val Ser Val Ala Ala Ser Ser His Val Pro Ile Xaa
                80                  85                  90
aar aag ctg cgt ttt gaa rac acc ctg gag ttt gta ggg ttt gat gcg      446
Lys Lys Leu Arg Phe Glu Xaa Thr Leu Glu Phe Val Gly Phe Asp Ala
            95                  100                 105
aar atg gct gar gaa tcc tcc tcc tcc tcc tcc tca tct tca cca ack      494
Lys Met Ala Glu Glu Ser Ser Ser Ser Ser Ser Ser Ser Ser Pro Thr
        110                 115                 120
gct gca aca tct cag cag cag caa ctt aaa aat aag agt ata ttg aat      542
Ala Ala Thr Ser Gln Gln Gln Gln Leu Lys Asn Lys Ser Ile Leu Asn
    125                 130                 135
ctc ttc tgt ggc ttc ggt gca tca tgc aaa cgg cct agc caa atc ttc      590
Leu Phe Cys Gly Phe Gly Ala Ser Cys Lys Arg Pro Ser Gln Ile Phe
140                 145                 150                 155
tac cac cgt ctc tagctttgct aacagcaaac ctggctctgc taagaagtta          642
Tyr His Arg Leu
gtgatcaaga actttaaaga taagcctaaa ttaccagaaa actacacaga tgaaacctgg    702
caaaaaaaaa aaa                                                      715
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<222> 120..185
<223> Von Heijne matrix
      score 6.30000019073486
      seq FALVWLWLRSTGC/FW
<223> polyA_signal
<222> 899..904
<223> polyA_site
<222> 918..931
<400> 140
aatttccggc gacacctcgc agtcattcct gcggcttgcg cgcccttgta gacagccggg     60
gccttcgtga gaccggtgca ggcctggggt agtctcctgt ctggacagag aagagaaaa      119
atg cag gga cac tgg ctc agt agt gcc ttt gca ttg gtt tgg ctt tgg       167
Met Gln Gly His Trp Leu Ser Ser Ala Phe Ala Leu Val Trp Leu Trp
       -20                 -15                 -10
cta cgc agc act ggt tgc ttc tgg tgg gat cat tgg cta tgt aaa agc      215
Leu Arg Ser Thr Gly Cys Phe Trp Trp Asp His Trp Leu Cys Lys Ser
   -5                  1                   5                  10
agg cag cgt gcc gtc cct ggc tgc agg gct gct ctt tgg cag tct agc      263
Arg Gln Arg Ala Val Pro Gly Cys Arg Ala Ala Leu Trp Gln Ser Ser
               15                  20                  25
cgg cct ggg tgc tta cca gct gtc tca gga tcc aag gaa cgt ttg ggt      311
Arg Pro Gly Cys Leu Pro Ala Val Ser Gly Ser Lys Glu Arg Leu Gly
           30                  35                  40
ttt cct agc tac atc tgg tac ctt ggc tgg cat tat ggg aat gag gtt      359
Phe Pro Ser Tyr Ile Trp Tyr Leu Gly Trp His Tyr Gly Asn Glu Val
       45                  50                  55
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cta cca ctc tgg aaa att cat gcc tgc agg ttt aat tgc agg tgc cag      407
Leu Pro Leu Trp Lys Ile His Ala Cys Arg Phe Asn Cys Arg Cys Gln
    60                  65                  70
ttt gct gat ggt cgc caa agt tgg agt tagtatgtkc aacagacccc            454
Phe Ala Asp Gly Arg Gln Ser Trp Ser
75                  80
attagcagaa gtcatgttcc agcttagatg atgaaraatt aaaaatctgc atcttccact    514
attttcaata tattaagaga aataagtgca gcatttttgc atctgacatt ttacctaaaa    574
aaaaaaacmc caaacttggc aaaaaggtgg aaaatcagtc atgattacaa acctacagag    634
gtggcgagta tgtaacacaa gagcttaata agaccctcat agagcttgat tcttgtatat    694
tgatgttgtc ttttctttct gtatctgtag gtaaatctca agggtaaaat gttaggtgtc    754
agctttcagg gctctgaaac cchattccct gctctgagga acagtgtgaa aaaaagtctt    814
ttaggaratt tacaatatct gttcttttgc tcatcttara ccacagactg actttgaaat    874
takgttaagt gaaatatcaa tgaaaataaa gtttactata aataawaaaa aaaaaaa       931
<210> 141
<211> 891
<212> DNA
<213> Homo sapiens
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<223> CDS
<222> 4..447
<223> sig_peptide
<222> 4..147
<223> Von Heijne matrix
      score 5.69999980926514
      seq LLLFFGKLLVVGG/VG
<223> polyA_signal
<222> 858..863
<223> polyA_site
<222> 880..891
<400> 141
atc atg atc gcc atc tac ggg aag aat ttc tgt gtc tca gcc aaa aat       48
    Met Ile Ala Ile Tyr Gly Lys Asn Phe Cys Val Ser Ala Lys Asn
                -45                 -40                 -35
gcg ttc atg cta ctc atg cga aac att gtc agg gtg gtc gtc ctg gac       96
Ala Phe Met Leu Leu Met Arg Asn Ile Val Arg Val Val Val Leu Asp
            -30                 -25                 -20
aaa gtc aca gac ctg ctg ctg ttc ttt ggg aag ctg ctg gtg gtc gga      144
Lys Val Thr Asp Leu Leu Leu Phe Phe Gly Lys Leu Leu Val Val Gly
        -15                 -10                 -5
ggc gtg ggg gtc ctg tcc ttc ttt ttt ttc tcc ggt cgc atc ccg ggg      192
Gly Val Gly Val Leu Ser Phe Phe Phe Phe Ser Gly Arg Ile Pro Gly
    1               5                   10                  15
ctg ggt aaa gac ttt aag agc ccc cac ctc aac tat tac tgg ctg ccc      240
Leu Gly Lys Asp Phe Lys Ser Pro His Leu Asn Tyr Tyr Trp Leu Pro
                20                  25                  30
ayc atg acc tcc atc ctg ggg gcc tat gtc atc gcc agy ggc ttc ttc      288
Xaa Met Thr Ser Ile Leu Gly Ala Tyr Val Ile Ala Ser Gly Phe Phe
            35                  40                  45
agc gtt ttc ggc atg tgt gtg gac acg ctc ttc ctc tgc ttc ctg gaa      336
Ser Val Phe Gly Met Cys Val Asp Thr Leu Phe Leu Cys Phe Leu Glu
        50                  55                  60
gac ctg gag cgg aca acg gct ccc tgg acg gcc cta cta cat gtc caa      384
Asp Leu Glu Arg Thr Thr Ala Pro Trp Thr Ala Leu Leu His Val Gln
    65                  70                  75
gag ctt cta aag att ctg ggc aag aag aac gag gcg ccc ccg gac aac      432
Glu Leu Leu Lys Ile Leu Gly Lys Lys Asn Glu Ala Pro Pro Asp Asn
80                  85                  90                  95
aag aaa agg aaa aak tgacagctcc ggccctgatc caggactgca ccccaccccc      487
Lys Lys Arg Lys Xaa
                100
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accgtccagc catccaacct cacttcgcct tacaggtctc cattttgtgg taaaaaaagg    547
ttttaggcca ggcgccgtgg ctcacgcctg twatccaaca ctttgaragg ctgaggcggg    607
cggatcacct kaktcaggak tycgagacca kcctggccaa catggtgaaa cctccgtctc    667
tattaaaaat acaaaaatta gccgagagtg gtggcatgca cctgtcatcc cagctactcg    727
ggaggctgag gcaggagaat cgcttgaacc cgggaggcag aggttgcagt gagccgagat    787
cgcgccactg cactccaacc tgggtgacag actctgtctc caaaacaaaa caaacaaaca    847
aaaagatttt attaaagata ttttgttaac tcaraaaaaa aaaa                     891
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<223> Von Heijne matrix
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      seq PLLGLLLSLPAGA/DV
<223> polyA_site
<222> 806..817
<400> 142
aaccgagctg gatttgtatg ttgcacc atg cct tct tgg atc ggg gct gtg att     54
                               Met Pro Ser Trp Ile Gly Ala Val Ile
                                                -20                 -15
ctt ccc ctc ttg ggg ctg ctg ctc tcc ctc ccc gcc ggg gcg gat gtg      102
Leu Pro Leu Leu Gly Leu Leu Leu Ser Leu Pro Ala Gly Ala Asp Val
                -10                 -5                  1
aag gct cgg agc tgc gga gag gtc cgc cag gcg tac ggt gcc aag gga      150
Lys Ala Arg Ser Cys Gly Glu Val Arg Gln Ala Tyr Gly Ala Lys Gly
        5                   10                  15
ttc agc ctg gcg gac atc ccc tac cag gag atc gca kgg gaa cac tta      198
Phe Ser Leu Ala Asp Ile Pro Tyr Gln Glu Ile Ala Xaa Glu His Leu
    20                  25                  30
aga atc tgt cct cag gaa tat aca tgc tgc acc aca gaa atg gar gac      246
Arg Ile Cys Pro Gln Glu Tyr Thr Cys Cys Thr Thr Glu Met Glu Asp
35                  40                  45                  50
aag tta agc caa caa agc aaa ctc gaa ttt gaa aac ctt gtg gaa gag      294
Lys Leu Ser Gln Gln Ser Lys Leu Glu Phe Glu Asn Leu Val Glu Glu
                55                  60                  65
aca agc cat ttt gtg cgc acc act ttt gtg tcc agg cat aag aaa ttt      342
Thr Ser His Phe Val Arg Thr Thr Phe Val Ser Arg His Lys Lys Phe
            70                  75                  80
gac gaw ttt ttc cga rag ctc ckg gag aat gca raa aag tca cta aat      390
Asp Xaa Phe Phe Arg Xaa Leu Xaa Glu Asn Ala Xaa Lys Ser Leu Asn
        85                  90                  95
gat rtg ttt gtm cgg acc tat ggc atg ctg tac wtg car aat kca gaa      438
Asp Xaa Phe Val Arg Thr Tyr Gly Met Leu Tyr Xaa Gln Asn Xaa Glu
    100                 105                 110
gtc ttc crg gac ctc ttc aca rag ctg aaa agg tac tac act ggg ggt      486
Val Phe Xaa Asp Leu Phe Thr Xaa Leu Lys Arg Tyr Tyr Thr Gly Gly
115                 120                 125                 130
aat gtg aat ctg gag gaa atg ctc aat gac ttt tgg gct cgg ctc ctg      534
Asn Val Asn Leu Glu Glu Met Leu Asn Asp Phe Trp Ala Arg Leu Leu
                135                 140                 145
gaa cgg atg ttt cag cwr awa aac cct cag tat cac ttc agt gaa gac      582
Glu Arg Met Phe Gln Xaa Xaa Asn Pro Gln Tyr His Phe Ser Glu Asp
            150                 155                 160
tac ctg gaa tgt gtg agc aaa tac act gac cak ctc aag cca ttt gga      630
Tyr Leu Glu Cys Val Ser Lys Tyr Thr Asp Xaa Leu Lys Pro Phe Gly
        165                 170                 175
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gac gtg ccc cgg aaa ctg aag att cag gtk acc cgc gcc ttc atk gsk      678
Asp Val Pro Arg Lys Leu Lys Ile Gln Val Thr Arg Ala Phe Xaa Xaa
    180                 185                 190
gcc agg acc ttt gtc cag ggg ctg act gtg ggc aga gaa gtt gca aac      726
Ala Arg Thr Phe Val Gln Gly Leu Thr Val Gly Arg Glu Val Ala Asn
195                 200                 205                 210
cga gtt tcc aag gta att gaa aac gtg ctt tct ttc tca ttg gtg ttc      774
Arg Val Ser Lys Val Ile Glu Asn Val Leu Ser Phe Ser Leu Val Phe
                215                 220                 225
ctt gtt tat tct gtt ttt aaa acc aat gtt taaaaaaaaa aaa               817
Leu Val Tyr Ser Val Phe Lys Thr Asn Val
            230                 235
<210> 143
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<223> Von Heijne matrix
      score 3.59999990463257
      seq SWLSLLAALAHLA/AA
<223> polyA_signal
<222> 988..993
<223> polyA_site
<222> 1009..1020
<400> 143
agtgggtcga kctggggcgc agtcgc atg ggg gag tct atc ccg ctg gcc gcc      53
                          Met Gly Glu Ser Ile Pro Leu Ala Ala
                                -60                 -55
ccg gtc ccg gtg gaa cag gcg gtg ctg gag acg ttc ttc tct cac ctg      101
Pro Val Pro Val Glu Gln Ala Val Leu Glu Thr Phe Phe Ser His Leu
            -50                 -45                 -40
ggt atc ttc tct tac gac aag gct aag gac aat gtg gag aag gaa cga      149
Gly Ile Phe Ser Tyr Asp Lys Ala Lys Asp Asn Val Glu Lys Glu Arg
        -35                 -30                 -25
gag gcc aac aag agc gcg ggg ggc agc tgg ctg tcg ctg ctg gcg gcc      197
Glu Ala Asn Lys Ser Ala Gly Gly Ser Trp Leu Ser Leu Leu Ala Ala
    -20                 -15                 -10
ttg gcg cac ctg gcc gcg gcc gag aag gtc tat cac agc ctc acc tac      245
Leu Ala His Leu Ala Ala Ala Glu Lys Val Tyr His Ser Leu Thr Tyr
-5                  1                   5                   10
ctg ggg cag aaa cta ggt acc tcc gcc ccg ccc ccc gag ccc ctt gag      293
Leu Gly Gln Lys Leu Gly Thr Ser Ala Pro Pro Pro Glu Pro Leu Glu
            15                  20                  25
gag gaa gta aag ggg gta tat tcc cca dtc ggc agt ggc ttg ggt btc      341
Glu Glu Val Lys Gly Val Tyr Ser Pro Xaa Gly Ser Gly Leu Gly Xaa
        30                  35                  40
ccg tct ctg tgt cac ttc tagtcgcagg ctcgactcgg cattcccaga             389
Pro Ser Leu Cys His Phe
    45
tctcctccca ccgttccttt ccttccctgg gcttccacaa gccccgccca ccrgcctgcr    449
ctgctgatag attggcgaac tgggtagatg ctctttgcaa ggctgtgacc caaaccgaaw    509
ggtttgccct tttgcctcgt gcatggattg atgccataaa tgagaagtta accaaaaaaa    569
aaaaacmcwd tycckktttm ccccccccgg grmcagaaga gcaaaacttt gcaaaacaac    629
ctagttctat tactgaacac tgttgtgtgg cctcttaagg ttaaggcccg agagtcacat    689
ttagagtcct accccgtctt catagtcccc caatacatat ttaatgacta aagtwataaa    749
tgaatattgg gcaggaaagg caagaaatat gcctaacact agcaagaaga gacttaaggg    809
gaaaatggta aacactctta gcacttcatg tacatcttgc ctctgaaata agattcaaga    869
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gctgattcaa ctgattttta ctagtagaag caataagtat aagtagatga gaaggaaata     929
atagatgtaa aaggcatgga atatgcatac aaaataatat tactgcttaa ttatgacaaa     989
taaatatatt ttgaatccta aaaaaaaaaa a                                   1020
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<222> 25..957
<223> sig_peptide
<222> 25..93
<223> Von Heijne matrix
      score 4.09999990463257
      seq LEAFSQAISAIQA/LR
<223> polyA_signal
<222> 1368..1373
<223> polyA_site
<222> 1388..1399
<400> 144
aakagctgct gtggcggcgg caac atg gcg gac gtg ata aat gtc agt gtg         51
                         Met Ala Asp Val Ile Asn Val Ser Val
                                        -20                 -15
aac ctg gag gcc ttt tcc cag gcc att agt gcc atc cag gcg ctg cga         99
Asn Leu Glu Ala Phe Ser Gln Ala Ile Ser Ala Ile Gln Ala Leu Arg
                -10                 -5                  1
tcc agc gtg agc agg gtg ttc gac tgc ctg aag gat ggg atg cgg aac        147
Ser Ser Val Ser Arg Val Phe Asp Cys Leu Lys Asp Gly Met Arg Asn
        5                   10                  15
aag gag acg ctg gag ggc cgg gag aag gcc ttt att gcg cac ttc cag        195
Lys Glu Thr Leu Glu Gly Arg Glu Lys Ala Phe Ile Ala His Phe Gln
    20                  25                  30
gac aac tta cat tcg gtc aac cgg gac ctc aat gag ctg gaa cgt ctg        243
Asp Asn Leu His Ser Val Asn Arg Asp Leu Asn Glu Leu Glu Arg Leu
35                  40                  45                  50
agc aat ctg gta ggc arg cca tct gar aac cat cct ctt cat aac agt        291
Ser Asn Leu Val Gly Xaa Pro Ser Glu Asn His Pro Leu His Asn Ser
                55                  60                  65
ggg ctg tta asc ctg gat cct gtg car gac aaa act cct ctc tat agt        339
Gly Leu Leu Xaa Leu Asp Pro Val Gln Asp Lys Thr Pro Leu Tyr Ser
            70                  75                  80
caa ctc ctt caa gca tat aag tgg tca aac aag ttg cag tac cat gca        387
Gln Leu Leu Gln Ala Tyr Lys Trp Ser Asn Lys Leu Gln Tyr His Ala
        85                  90                  95
gga cta gca tct ggc ctt tta aat cas car tca ktg aag cgt ycc gct        435
Gly Leu Ala Ser Gly Leu Leu Asn Xaa Gln Ser Xaa Lys Arg Xaa Ala
    100                 105                 110
aat cag atg gga gta tct gcc aaa cgt aga cca aag gct cag ccc aca        483
Asn Gln Met Gly Val Ser Ala Lys Arg Arg Pro Lys Ala Gln Pro Thr
115                 120                 125                 130
act ctt gtc cta cca cct caa tat gtt gat gat gtg atc agc cgc att        531
Thr Leu Val Leu Pro Pro Gln Tyr Val Asp Asp Val Ile Ser Arg Ile
                135                 140                 145
gac agg atg ttt cct gaa atg tcc atc cac tta tcc aga ccc aat gga        579
Asp Arg Met Phe Pro Glu Met Ser Ile His Leu Ser Arg Pro Asn Gly
            150                 155                 160
aca tca gca atg ctt ctg gtg acc ttg gga aar gtg ttg aaa gtg awc        627
Thr Ser Ala Met Leu Leu Val Thr Leu Gly Lys Val Leu Lys Val Xaa
        165                 170                 175
gtc gtc rtr cgg arm ctg ttc att gat cga aca ata gtw aag gga tat        675
Val Val Xaa Arg Xaa Leu Phe Ile Asp Arg Thr Ile Val Lys Gly Tyr
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    180                 185                 190
wac gag aat gtc tac rca gaa kat ggc mag ctt gat ata tgg tcc aaa      723
Xaa Glu Asn Val Tyr Xaa Glu Xaa Gly Xaa Leu Asp Ile Trp Ser Lys
195                 200                 205                 210
tcc aac tat caa gta ttc cag aag gtg aca gac cat gcc acc act gcc      771
Ser Asn Tyr Gln Val Phe Gln Lys Val Thr Asp His Ala Thr Thr Ala
                215                 220                 225
ctg ctc cac taw mag ctg ccc cag atg ccg gat gtc gtg gtc cga tcc      819
Leu Leu His Xaa Xaa Leu Pro Gln Met Pro Asp Val Val Val Arg Ser
            230                 235                 240
ttc awg acc tgg tta aga agt tac ata aag ctg ttc cag gcc ccg tgc      867
Phe Xaa Thr Trp Leu Arg Ser Tyr Ile Lys Leu Phe Gln Ala Pro Cys
        245                 250                 255
cag cgc tgc ggg aag ttt ctg cag gac ggc ctt ccc ccg aca tgg agg      915
Gln Arg Cys Gly Lys Phe Leu Gln Asp Gly Leu Pro Pro Thr Trp Arg
    260                 265                 270
gat ttc cga acc ctc gaa gcc ttc cat gac acc tgc cgg cag              957
Asp Phe Arg Thr Leu Glu Ala Phe His Asp Thr Cys Arg Gln
275                 280                 285
tagcccccac gctggcccca gcctcagacc ccacccagca ccttcccaga cacgcaggaa   1017
gcccacagaa ggctcagctg gttcctcact gcccagatgt gtacagctgc tcctcccttt   1077
cataaagcag cgccatgtgt gcagaggcca ctcttgaaga gcagactccc tctgtggctg   1137
atgggactaa ttattcccac tagccagcgg actgaaggca aagaagacct ttctagaacc   1197
tggtagaagg aagctgtgca gcatgctcct cgtccatgtg tgtcggcagt gctggtgtct   1257
gtcgtctccg cgagctgtta ctggaatgag cccttgtgtt catgggtatc gtcatgcggg   1317
gttcttgtgt tttgtggggc ttgggttttg gttaacttat ttttataagc aataaacctt   1377
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                                                  Met Thr Ser
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ttg ttt gct gtt gtg tta cag aga gag aag gaa cct cac ctg tgg ctc      103
Leu Phe Ala Val Val Leu Gln Arg Glu Lys Glu Pro His Leu Trp Leu
        -55                 -50                 -45
agc tca ccc cac atc cgt ttc tca tta cgt gta aat aaa ctg tca gag      151
Ser Ser Pro His Ile Arg Phe Ser Leu Arg Val Asn Lys Leu Ser Glu
    -40                 -35                 -30
ctg atg tta cag ctt tta cag ttt aaa gca ttc ccc tcg tct cta gtt      199
Leu Met Leu Gln Leu Leu Gln Phe Lys Ala Phe Pro Ser Ser Leu Val
-25                 -20                 -15                 -10
cct ttt ttc ttg ttt aca tgt ttt ggg cac ttt ccc tca ttc acc acc      247
Pro Phe Phe Leu Phe Thr Cys Phe Gly His Phe Pro Ser Phe Thr Thr
                -5                  1                   5
ttc cag ggc ttc ata gaa aat aac ttg tta caa aat cag ttc aat tct      295
Phe Gln Gly Phe Ile Glu Asn Asn Leu Leu Gln Asn Gln Phe Asn Ser
        10                  15                  20
aat gtg gac ata gtg gca tgt tca taattagacc catatagggg acactgagct     349
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Asn Val Asp Ile Val Ala Cys Ser
    25                  30
ttaaatcgtt gattctaaac tctatacatt aaaaaaattc agcccaggcc cctcaaagcc    409
tgaraaaatt taatttgctc ttaatttaat gttccaaaac tcactcttgg aaaaatgcct    469
gttggaaaac tacaggtggg tcacatgtkg gggctgtctc cgtgacactc aggattccag    529
tcaraaccta atcctcatat ctattgccta caaaaataga ccaagaatgt tgctgctctt    589
ttataatcct ttaaatattt aacattcaag ttttctttgt cttaaattca gcctcttcct    649
aaaagcaaaa aaaaaaa                                                   666
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amggagcaga acagagagc atg gag ctg gag agg atc gtc agt gca gcc ctc     112
                    Met Glu Leu Glu Arg Ile Val Ser Ala Ala Leu
                        -15                 -10
ctt gcc ttt gtc cag aca cac ctc ccg gag gcc gac ctc agt ggc ttg      160
Leu Ala Phe Val Gln Thr His Leu Pro Glu Ala Asp Leu Ser Gly Leu
    -5                  1               5                   10
gat gag gtc atc ttc tcc tat gtg ctt ggg gtc ctg gag gac ctg ggc      208
Asp Glu Val Ile Phe Ser Tyr Val Leu Gly Val Leu Glu Asp Leu Gly
                15                  20                  25
ccc tcg ggc cca tca gag gag aac ttc gat atg gag gct ttc act gag      256
Pro Ser Gly Pro Ser Glu Glu Asn Phe Asp Met Glu Ala Phe Thr Glu
            30                  35                  40
atg atg gag gcc tat gtg cct ggc ttc gcc cac atc ccc agg ggc aca      304
Met Met Glu Ala Tyr Val Pro Gly Phe Ala His Ile Pro Arg Gly Thr
        45                  50                  55
ata ggg gac atg atg cag aar ctc tca ggg cag ctg agc gat gcc vgg      352
Ile Gly Asp Met Met Gln Lys Leu Ser Gly Gln Leu Ser Asp Ala Xaa
    60                  65                  70
aac aaa gag aac ctg caa ccg cag aac tct ggt gtc caa ggt cag gtg      400
Asn Lys Glu Asn Leu Gln Pro Gln Asn Ser Gly Val Gln Gly Gln Val
75                  80                  85                  90
ccc atc tcc cca gag ccc ctg cag cgg ccc gaa atg ctc aaa gaa gag      448
Pro Ile Ser Pro Glu Pro Leu Gln Arg Pro Glu Met Leu Lys Glu Glu
                95                  100                 105
act agg tct tcg gct gct gct gct gca gac acc caa gat gag gca act      496
Thr Arg Ser Ser Ala Ala Ala Ala Ala Asp Thr Gln Asp Glu Ala Thr
            110                 115                 120
ggc gct gag gag gag ctt ctg cca ggg gtg gat gta ctc ctg gag gtg      544
Gly Ala Glu Glu Glu Leu Leu Pro Gly Val Asp Val Leu Leu Glu Val
        125                 130                 135
ttc cct acc tgt tcg gtg gag cag gcc cag tgg gtg ctg gcc aaa gct      592
Phe Pro Thr Cys Ser Val Glu Gln Ala Gln Trp Val Leu Ala Lys Ala
    140                 145                 150
cgg ggg gac ttg gaa gaa gct gtg cag atg ctg gta gag gga aag gaa      640
Arg Gly Asp Leu Glu Glu Ala Val Gln Met Leu Val Glu Gly Lys Glu
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155                 160                 165                 170
gag ggg cct gca gcc tgg gag ggc ccc aac cag gac ctg ccc aga cgc      688
Glu Gly Pro Ala Ala Trp Glu Gly Pro Asn Gln Asp Leu Pro Arg Arg
                175                 180                 185
ctc aga ggc ccc caa aag gat gag ctg aag tcc ttc atc ctg cag aag      736
Leu Arg Gly Pro Gln Lys Asp Glu Leu Lys Ser Phe Ile Leu Gln Lys
            190                 195                 200
tac atg atg gtg gat agc gca gag gat cag aag att cac cgg ccc atg      784
Tyr Met Met Val Asp Ser Ala Glu Asp Gln Lys Ile His Arg Pro Met
        205                 210                 215
gct ccc aag gag gcc ccc aag aag ctg atc cga tac atc gac aac cag      832
Ala Pro Lys Glu Ala Pro Lys Lys Leu Ile Arg Tyr Ile Asp Asn Gln
    220                 225                 230
gta gtg agc acc aaa ggg gag cga ttc aaa gat gtg cgg aac cct gag      880
Val Val Ser Thr Lys Gly Glu Arg Phe Lys Asp Val Arg Asn Pro Glu
235                 240                 245                 250
gcc gag gag atg aag gcc aca tac atc aac ctc aag cca gcc aga aag      928
Ala Glu Glu Met Lys Ala Thr Tyr Ile Asn Leu Lys Pro Ala Arg Lys
                255                 260                 265
tac cgc ttc cat tgaggcactc gccggactct gcccgagcct tctaggctca          980
Tyr Arg Phe His
            270
gatcccagag ggatgcagga gccctatacc cctacacagg ggccccctaa ctcctgtccc   1040
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ggagacccag catagccagg ccagt atg gag cac ctc acg cac agc tct cag      172
                          Met Glu His Leu Thr His Ser Ser Gln
                                                  -45
aag ctg cag gcg gac gaa cat ctg acc aaa gag gtg tgg tcg agg ctc      220
Lys Leu Gln Ala Asp Glu His Leu Thr Lys Glu Val Trp Ser Arg Leu
-40                 -35                 -30                 -25
ctg aaa gag aaa ggg cct gct ggt ctc atc ctc tgc ttc ctt tgc ctt      268
Leu Lys Glu Lys Gly Pro Ala Gly Leu Ile Leu Cys Phe Leu Cys Leu
                -20                 -15                 -10
tac cct ata cct ctc tgc acg tcc cac ccc gtt tkg ctg tgt gcy cac      316
Tyr Pro Ile Pro Leu Cys Thr Ser His Pro Val Xaa Leu Cys Ala His
            -5                  1                   5
ccc cag gat gtg tac ccg gtt gta gta aga gct gaa atc cat gct gag      364
Pro Gln Asp Val Tyr Pro Val Val Val Arg Ala Glu Ile His Ala Glu
    10                  15                  20
ctg tac cag gaa ctt gca tat cta aaa aca gaa act gag tca ctg gcc      412
Leu Tyr Gln Glu Leu Ala Tyr Leu Lys Thr Glu Thr Glu Ser Leu Ala
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25                  30                  35                  40
cat ctc ttt gct ctt gtg ccc cag gcc aaa ata aag aat aga gtg          457
His Leu Phe Ala Leu Val Pro Gln Ala Lys Ile Lys Asn Arg Val
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taragtgaaa aaaaaaaa                                                  475
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gaatgtattt actatcattt tgttttacta tagaggtag atg gga ctc tta act       114
                                        Met Gly Leu Leu Thr
                                           -35
ttt ggg tac att gaa amc akg ckg aaa act gaa cac aat cct gat cat      162
Phe Gly Tyr Ile Glu Xaa Xaa Xaa Lys Thr Glu His Asn Pro Asp His
    -30                 -25                 -20
cac tcc tgc ctg gct gtc tcc tgg gag gct gcc ggg tgc cac gga gct      210
His Ser Cys Leu Ala Val Ser Trp Glu Ala Ala Gly Cys His Gly Ala
-15                 -10                 -5                  1
ggg aca cag cag agc ccg cta ggt gtt gca ggg ccc tgg agg cca agg      258
Gly Thr Gln Gln Ser Pro Leu Gly Val Ala Gly Pro Trp Arg Pro Arg
            5                   10                  15
cca ccc tgt gtg ggg tcc ctg ttg gca gcc agg tcc cta cac aaa caa      306
Pro Pro Cys Val Gly Ser Leu Leu Ala Ala Arg Ser Leu His Lys Gln
        20                  25                  30
gta atc ctg ttt ggc ctc cta ggt ttt gca tat gac cac gca gcc          351
Val Ile Leu Phe Gly Leu Leu Gly Phe Ala Tyr Asp His Ala Ala
    35                  40                  45
taatttgggg tgtaggggaa cctctgctgg cccttgctcc tttgtatgtt gggtgacttt    411
aatggctggc cacatacccc tttctcccag ctactcattc actgacttgg gtaagttcta    471
gcacaatgcg cacttagaaa cagaatgtga cacatcaaca ttaacttttc ctgaaaagaa    531
cagtttgcct aacatggacc cmaaagaagc ttggaattta taagactttc ctttataaga    591
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tgcctcccag gttcatgcca ttctcctgcc tcancctccc gagtagctgg gactacaggt    771
gtctgccgcc acgcctggct aatttttttg tatttttagt agagacgggg tttcaccatg    831
ttggtcagga tggtctcgat ttcctgacct cgtgatccgc ctgtctcggc ctcccaaagt    891
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cactagtggg tgggattgag gtatgccctg gtgcataaat agagactcag ctgtgctggc 120
acactcagaa gcttggaccg catcctagcc gccgactcac acaaggcaga gttgcc atg 179
Met
-20
gaa aaa att cca gtg tca gca ttc ttg ctc ctt gtg gcc ctc tcc tac 227
Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser Tyr
-15 -10 -5
act ctg gcc aga gat acc aca gtc aaa cct gga gcc aaa aag gac aca 275
Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp Thr
1 5 10
aag gac tct cga ccc aaa ctg ccc cag acc ctc tcc aga ggt tgg ggt 323
Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp Gly
15 20 25
gac caa ctc atc tgg aca car aca tat gaa raa rct cta twt aaa tcc 371
Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Xaa Xaa Leu Xaa Lys Ser
30 35 40 45
aar aca agc aac aaa ccc ttg atg att att cat cac ttg gat gad tgc 419
Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Xaa Cys
50 55 60
cca cac agt caa gct tta aaa aaa ktg ttt gct gaa aat aaa raa atc 467
Pro His Ser Gln Ala Leu Lys Lys Xaa Phe Ala Glu Asn Lys Xaa Ile
65 70 75
cag aaa ttg gca ran cag ttt gtc cyc ctc aat ctg gtt tat gaa aca 515
Gln Lys Leu Ala Xaa Gln Phe Val Xaa Leu Asn Leu Val Tyr Glu Thr
80 85 90
act gac aaa cac ctt tct cct gat ggc caa tat ktc ccc cmg gat tat 563
Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Xaa Pro Xaa Asp Tyr
95 100 105
gtt tgt tgacccatct ctgacagtta gagccgatat cactggaaga tattcaaayc 619
Val Cys
110
gtctctatgc ttacgaacct gcagatacag ctctgttgct tgacaacatg aagaaagctc 679
tcaagttgct gaagactgaa ttgtaaagaa aaaaaatctc caagcccttc tgtctgtcag 739
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acacactgat taggttatgg tttaatgtta caacaactat tttttaagaa aaacaagttt 859
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Met Met Asn Phe Arg Gln Arg Met Gly Trp Ile Gly Val Gly

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                  -20                 -15                 -10
ttg tat ctg tta gcc agt gca gca gca ttt tac tat gtt ttt gaa atc      156
Leu Tyr Leu Leu Ala Ser Ala Ala Ala Phe Tyr Tyr Val Phe Glu Ile
                -5                  1                   5
agt gag act tac aac agg ctg gcc ttg gaa cac att caa cag cac cct      204
Ser Glu Thr Tyr Asn Arg Leu Ala Leu Glu His Ile Gln Gln His Pro
        10                  15                  20
ggg gag ccc ctt gaa gga acc aca tgg aca cac tcc ttg aaa gct caa      252
Gly Glu Pro Leu Glu Gly Thr Thr Trp Thr His Ser Leu Lys Ala Gln
    25                  30                  35
tta ctc tcc ttg cct ttt tgg gtg tgg aca gtt att ttt ctg gta cct      300
Leu Leu Ser Leu Pro Phe Trp Val Trp Thr Val Ile Phe Leu Val Pro
40                  45                  50                  55
tac tta car atk ttt ttg ttc cta tac tct tgt aca aaa vct gat ccc      348
Tyr Leu Gln Xaa Phe Leu Phe Leu Tyr Ser Cys Thr Lys Xaa Asp Pro
                60                  65                  70
aaa aca gtg ggc tac tgt wtc atc cct ata tgc ttg gca rtt att tsc      396
Lys Thr Val Gly Tyr Cys Xaa Ile Pro Ile Cys Leu Ala Xaa Ile Xaa
            75                  80                  85
aat cgc cac cag gat ttt gtc aag gct tct aat caa atc agc aaa cta      444
Asn Arg His Gln Asp Phe Val Lys Ala Ser Asn Gln Ile Ser Lys Leu
        90                  95                  100
caa ctg att gac acg taaaatcagt caccgttttt tccctacgat tacaaaactg      499
Gln Leu Ile Asp Thr
    105
ccagtcctat atggagtctg atcacaagac tgcagtttct tcacagatct caggaagttg     559
tcgtggggca gaggcttttt aaaaacatgt gattagggag ctatctttat ctgaataata     619
acgaattttt aggtaaaacc tgagatagag tactacaaaa tcatgttgat gacttcagat     679
tttggaagtt aaatcatgtc tgttatttgc attctttaga aacttgacta agtacctgaa     739
ttcatatttc tattctactg tgcaacatag tgatgattca gaaatttttc ctttggggaa     799
aaaaatgaat atgaacattt ccattgtgtt aagtgtaaaa aggtccagka catgatcata     859
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     Met Ala Val Phe Val Val Leu Leu Ala Leu Val Ala Gly Val Leu
         -15                 -10                 -5
ggg aac gag ttt agt ata tta aaa tca cca ggg tct gtt gtt ttc cga      157
Gly Asn Glu Phe Ser Ile Leu Lys Ser Pro Gly Ser Val Val Phe Arg
    1               5                   10                  15
aat gga aat tgg cct ata cca gga gag cgg atc cca gac gtg gct gca      205
Asn Gly Asn Trp Pro Ile Pro Gly Glu Arg Ile Pro Asp Val Ala Ala
                20                  25                  30
ttg tcc atg ggc ttc tct gtg aaa gaa gac ctt tct tgg cca gga ctc      253
Leu Ser Met Gly Phe Ser Val Lys Glu Asp Leu Ser Trp Pro Gly Leu
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            35                  40                  45
gca gtg ggt aac ctg ttt cat cgt cct cgg gct agc gtc atg gtg atg      301
Ala Val Gly Asn Leu Phe His Arg Pro Arg Ala Ser Val Met Val Met
        50                  55                  60
gtg aag gga gtt aac aac tmc cct cta ccc cca ggc tgt gtc att tcg      349
Val Lys Gly Val Asn Asn Xaa Pro Leu Pro Pro Gly Cys Val Ile Ser
    65                  70                  75
tac cct ttg gag aat gca gtt cct ttt agt ctt gac agt gtt gca aat      397
Tyr Pro Leu Glu Asn Ala Val Pro Phe Ser Leu Asp Ser Val Ala Asn
80                  85                  90                  95
tcc att cac tcc tta ttt tct gag gaa act cct gtt gtt ttg cag ttg      445
Ser Ile His Ser Leu Phe Ser Glu Glu Thr Pro Val Val Leu Gln Leu
                100                 105                 110
gct ccc agt gag gaa aga gtg tat atg gta ggg aag gcm aac tca gtg      493
Ala Pro Ser Glu Glu Arg Val Tyr Met Val Gly Lys Ala Asn Ser Val
            115                 120                 125
tgg aar acc ttt cag tca ctt gcg cca gct ccg kta atc rcc tgt ttc      541
Trp Lys Thr Phe Gln Ser Leu Ala Pro Ala Pro Xaa Ile Xaa Cys Phe
        130                 135                 140
aag aaa act ctg ttc tca gtt cac tcc ccc ycc att cma ctg agt agg      589
Lys Lys Thr Leu Phe Ser Val His Ser Pro Xaa Ile Xaa Leu Ser Arg
    145                 150                 155
aac aat gaa gtt gac cyg ctc ttt ctt tct gaa ctg caa gtg cta cat      637
Asn Asn Glu Val Asp Xaa Leu Phe Leu Ser Glu Leu Gln Val Leu His
160                 165                 170                 175
gat att tca agc ttg ctg tct cgt cat aag cat cta gcc aag gat cat      685
Asp Ile Ser Ser Leu Leu Ser Arg His Lys His Leu Ala Lys Asp His
                180                 185                 190
tct cct gat tta tat tca ctg gag ctg gca ggt ttg gat gaa att ggg      733
Ser Pro Asp Leu Tyr Ser Leu Glu Leu Ala Gly Leu Asp Glu Ile Gly
            195                 200                 205
aag cgt tat ggg gaa gac tct gaa caa ttc aga gat gct tct aag atc      781
Lys Arg Tyr Gly Glu Asp Ser Glu Gln Phe Arg Asp Ala Ser Lys Ile
        210                 215                 220
ctt gtt gac gct ctg caa aag ttt gca gat gac atg tac agt ctt tat      829
Leu Val Asp Ala Leu Gln Lys Phe Ala Asp Asp Met Tyr Ser Leu Tyr
    225                 230                 235
ggt ggg aat gca gtg gta gag tta gtc act gtc aag tca ttt gac acc      877
Gly Gly Asn Ala Val Val Glu Leu Val Thr Val Lys Ser Phe Asp Thr
240                 245                 250                 255
tcc ctc att agg aag aca agg act atc ctt gag gca aaa caa gcg aag      925
Ser Leu Ile Arg Lys Thr Arg Thr Ile Leu Glu Ala Lys Gln Ala Lys
                260                 265                 270
aac cca gca agt ccc tat aac ctt gca tat aag tat aat ttt gaa tat      973
Asn Pro Ala Ser Pro Tyr Asn Leu Ala Tyr Lys Tyr Asn Phe Glu Tyr
            275                 280                 285
tcc gtg gtt ttc aac atg gta ctt tgg ata atg atc gcc ttg gcc ttg     1021
Ser Val Val Phe Asn Met Val Leu Trp Ile Met Ile Ala Leu Ala Leu
        290                 295                 300
gct gtg att atc acc tct tac aat att tgg aac atg gaa tcc tgg ata     1069
Ala Val Ile Ile Thr Ser Tyr Asn Ile Trp Asn Met Glu Ser Trp Ile
    305                 310                 315
tgatagcatc atttatagga tgacaaacca gaagattcgg aatggattga atgttacctg   1129
tgccagaatt akaaaagggg gttggaaatt ggctgttttg ttaaaatata tcttttagtg   1189
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cattctgttt aatgaatttg gaaatatgca ctgaaagaaa tgtaaaacat ttagaatagc   1429
tcgtgttatg gaaaaaagtg cactgaattt attagacaaa cttacgaatg cttaacttct   1489
ttacacagca taggtgaaaa tcatatttgg gctattgtat actatgaaca atttgtaaat   1549
gtcttaattt gatgtaaata actctgaaac aagagaaaag gtttttaact tagagtagcc   1609
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ctaaaatatg gatgtgctta tataatcgct tagttttgga actgtatctg agtaacagag   1669
gacagctgtt ttttaaccct cttctgcaag tttgttgacc tacatgggct aatatggata   1729
ctaaaaatac tacattgatc taagaagaaa ctagccttgt ggagtatata gatgcttttc   1789
attatacaca caaaaatccc tgagggacat tttgaggcat gaatataaaa catttttatt   1849
tcagtaactt ttccccctgt gtaagttact atggtttgtg gtacaacttc attctataga   1909
atattaagtg gaagtgggtg aattctactt tttatgttgg agtggaccaa tgtctatcaa   1969
gagtgacaaa taaagttaat gatgattcca aaaaaaaaaa a                       2010
<210> 152
<211> 387
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<222> 70..321
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<222> 70..234
<223> Von Heijne matrix
      score 4.09999990463257
      seq AVCAALLASHPTA/EV
<223> polyA_signal
<222> 364..369
<223> polyA_site
<222> 375..387
<400> 152
agaaatcgta ggacttccga aagcagcggc ggcgtttgct tcactgcttg gaagtgtgag     60
tgcgcgaag atg cga aag gtg gtt ttr att acc ggg gct agc agt ggc att    111
          Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile
          -55                 -50                 -45
ggc ctg gcc ctc tgc aag cgg ctg ctg gcg gaa gat gat gag ctt cat     159
Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His
    -40                 -35                 -30
ctg tgt ttg gcg tgc agg aat atg agc aag gca gaa gct gtc tgt gct     207
Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala
-25                 -20                 -15                 -10
gct ctg ctg gcc tct cac ccc act gct gag gtc acc att gtc cag gtg     255
Ala Leu Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val
                -5                  1                   5
gat gtc agc aac ctg cag tca ttc ttc cgg gcc tcc aag gaa ctt aag     303
Asp Val Ser Asn Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys
        10                  15                  20
caa agg atg atc tct tgc tgatggattt tttttctcat gtgattgtgc           351
Gln Arg Met Ile Ser Cys
    25
ascataacac ttaataaaat aagaaaaaaa aaaaaa                            387
<210> 153
<211> 983
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<223> CDS
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<223> sig_peptide
<222> 38..91
<223> Von Heijne matrix
      score 7.40000009536743
      seq GWLVLCVLAISLA/SM
<223> polyA_signal
<222> 947..952
<223> polyA_site
<222> 974..983
<400> 153
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aatccagtyg gasttgacaa caggaggcag aggcatc atg gag ggt ccc cgg gga      55
                                        Met Glu Gly Pro Arg Gly
                                                        -15
tgg ctg gtg ctc tgt gtg ctg gcc ata tcg ctg gcc tct atg gtg acc      103
Trp Leu Val Leu Cys Val Leu Ala Ile Ser Leu Ala Ser Met Val Thr
        -10                 -5                  1
gag gac ttg tgc cga gca cca gac ggg aag aaa ggg gag gca gga aga      151
Glu Asp Leu Cys Arg Ala Pro Asp Gly Lys Lys Gly Glu Ala Gly Arg
5                   10                  15                  20
cct ggc aga cgg ggg cgg cca ggc ctc aag ggg gag caa ggg gag ccg      199
Pro Gly Arg Arg Gly Arg Pro Gly Leu Lys Gly Glu Gln Gly Glu Pro
                25                  30                  35
ggg gcc cct ggc atc cgg aca ggc atc caa ggc ctt aaa gga gac cag      247
Gly Ala Pro Gly Ile Arg Thr Gly Ile Gln Gly Leu Lys Gly Asp Gln
            40                  45                  50
ggg gaa cct ggg ccc tct gga aac ccc ggc aag gtg ggc tac cca ggg      295
Gly Glu Pro Gly Pro Ser Gly Asn Pro Gly Lys Val Gly Tyr Pro Gly
        55                  60                  65
ccc agc ggc ccc ctc gga gcc cgt ggc atc ccg gga att aaa ggc acc      343
Pro Ser Gly Pro Leu Gly Ala Arg Gly Ile Pro Gly Ile Lys Gly Thr
    70                  75                  80
aag ggc agc cca gga aac atc aag gac cag ccg agg cca gcc ttc tcc      391
Lys Gly Ser Pro Gly Asn Ile Lys Asp Gln Pro Arg Pro Ala Phe Ser
85                  90                  95                  100
gcc att cgg cgg aac ccc cca atg ggg ggc aac gtg gtc atc ttc gac      439
Ala Ile Arg Arg Asn Pro Pro Met Gly Gly Asn Val Val Ile Phe Asp
                105                 110                 115
acg gtc atc acc aac cag gaa gaa ccg tac cag aac cac tcc ggc cga      487
Thr Val Ile Thr Asn Gln Glu Glu Pro Tyr Gln Asn His Ser Gly Arg
            120                 125                 130
ttc gtc tgc act gta ccc gct act act act tca cct tcc agg tgc tgt      535
Phe Val Cys Thr Val Pro Ala Thr Thr Thr Ser Pro Ser Arg Cys Cys
        135                 140                 145
ccc agt ggg aaa tct gcc tgt cca tcg tct cct cct caa ggg gcc agg      583
Pro Ser Gly Lys Ser Ala Cys Pro Ser Ser Pro Pro Gln Gly Ala Arg
    150                 155                 160
tcc gac gct ccc tgg gct tct gtg aca cca cca aca agg ggc tct tcc      631
Ser Asp Ala Pro Trp Ala Ser Val Thr Pro Pro Thr Arg Gly Ser Ser
165                 170                 175                 180
agg tgg tgt cag ggg gca tgg tgc ttc agc tgc agc agg gtg acc agg      679
Arg Trp Cys Gln Gly Ala Trp Cys Phe Ser Cys Ser Arg Val Thr Arg
                185                 190                 195
tct ggg ttg aaa aag acc cca aaa agg gtc aca ttt acc agg gct ctg      727
Ser Gly Leu Lys Lys Thr Pro Lys Arg Val Thr Phe Thr Arg Ala Leu
            200                 205                 210
agg ccg aca gcg tct tca gcg gct tcc tca tct tcc cat ctg cct gag      775
Arg Pro Thr Ala Ser Ser Ala Ala Ser Ser Ser Ser His Leu Pro Glu
        215                 220                 225
cca ggg aag gac ccc ctc ccc cac cca cct ctc tgg ctt cca tgc tcc      823
Pro Gly Lys Asp Pro Leu Pro His Pro Pro Leu Trp Leu Pro Cys Ser
    230                 235                 240
gcc tgt aaa atg ggg gcg cta ttg ctt cag ctg ctg aag gga ggg ggc      871
Ala Cys Lys Met Gly Ala Leu Leu Leu Gln Leu Leu Lys Gly Gly Gly
245                 250                 255                 260
tgg ctc tgagagcccc aggactggct gccccgtgac acatgctcta agaagctcgt      927
Trp Leu
ttcttagacc tcttcctgga ataaacatct gtgtctgtgt ctgctgaaaa aaaaaa       983
<210> 154
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<220>
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<222> 51..470
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<222> 51..203
<223> Von Heijne matrix
score 5.80000019073486
seq AVGLFPAPTECFA/RV
<223> polyA_signal
<222> 1585..1590
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<222> 1604..1614
<400> 154

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ataagcctgt ggttgatgga aattcacaaa gtgaggcatt atcactggaa atg aga        56
                                                        Met Arg
                                                           -50
aag gat ccg agc ggg gct ggc ctc tgg ctt cac agt ggc ggc cca gtg      104
Lys Asp Pro Ser Gly Ala Gly Leu Trp Leu His Ser Gly Gly Pro Val
            -45                 -40                 -35
ctt cca tat gtg aga gaa tca gta aga aga aat cca gcc tca gca gcc      152
Leu Pro Tyr Val Arg Glu Ser Val Arg Arg Asn Pro Ala Ser Ala Ala
        -30                 -25                 -20
act ccg agc aca gcc gtg ggt ttg ttc cct gct cca aca gag tgt ttt      200
Thr Pro Ser Thr Ala Val Gly Leu Phe Pro Ala Pro Thr Glu Cys Phe
    -15                 -10                 -5
gct cgg gtg tcc tgc agt ggt gtt gaa gct ctg ggg cgg cga gac tgg      248
Ala Arg Val Ser Cys Ser Gly Val Glu Ala Leu Gly Arg Arg Asp Trp
 1               5                  10                  15
ctg gga gga ggg ccc agg gcc cac tgr msg gcv aca gag gmc agt gcc      296
Leu Gly Gly Gly Pro Arg Ala His Xaa Xaa Ala Thr Glu Xaa Ser Ala
            20                  25                  30
cca aag gag agc ctc ggg tgt cac gac tgc cac gcc atc aaa aag tgc      344
Pro Lys Glu Ser Leu Gly Cys His Asp Cys His Ala Ile Lys Lys Cys
        35                  40                  45
cgg aaa tgg gaa gtt ttc agg atg acc cac caa gtg ctt ttc cca agg      392
Arg Lys Trp Glu Val Phe Arg Met Thr His Gln Val Leu Phe Pro Arg
    50                  55                  60
gtc tgg gct ctg agt tgg aac ccg ctt gcc tgc act cca tcc tgt ctg      440
Val Trp Ala Leu Ser Trp Asn Pro Leu Ala Cys Thr Pro Ser Cys Leu
65                  70                  75
caa cgc tgc aca tgt atc ccg aak tgc tcc tgagtgagga racaaaacgc        490
Gln Arg Cys Thr Cys Ile Pro Xaa Cys Ser
80                  85
atktyccttg accgtytaaa gcccatgttt ycaaagcaaa caatavaatt caaraarrtg    550
cttaaaagca cctcaratgg tckgcaaata acactggggt tactggctct gcaacctttt    610
gaattavcaa atacattatg ccatagttaa ggtacaagca gaacaatacc aatagattaa    670
ttttaagagt tgtcttagaa tgatttcttt cgcataaagt ctggatgcaa actgtgcagc    730
ccttaggtmc ctgctgtagt tttgtacgac ctggcagact taaagtaaat tgagtttaaa    790
ttcaaagcca gttgatgcgg aaggaacttt tttggcatgt gttaaattgt gctttaaaag    850
acatataaag aattgggaaa catttcagga gacgatcata gcctgtataa ataccagatt    910
agaacatacg gatttaccat gaagttctgt cttcaacatc cattctaaag ggctactgtc    970
ccaaatcctg tgtgtccttt tgacttgtct gatcacccaa tggaagtgga tacttgtaaa   1030
gtctacacca ctgtacttgg cgttaaatct tgctgaattc gtggtaagct gttaccatgt   1090
ctacattttg tagaatgatt ttggtctgca gcaaaattcg atttcacttc tcatacccct   1150
ttccttccac ttgaaatgca atttagacag akgccctgtg gtgaaagttg caatattaag   1210
tttaccttta gaagatccct tctcaaactc agaaccctag cagtgttacc ttaaacaaaa   1270
atgakctcga gaaaaaagta gctcagttac agagaagcaa atcgagttat ttcccacata   1330
aaaagtttcc cagattctaa gaattgcagt atcctgtacc ctaaaatttt tcaaggtgac   1390
tcctgttgtc gtctgttgat aactttaata aaggtcattt aaggacataa gtttttaaag   1450
actcccaaag tgaaacttaa acattttcgg gattatcgat tgcatatatc agtttatgct   1510
gtgtgctgaa ttactatgcc atgtgctatt ttagtgtttg gggaaaatga aaaataaaat   1570
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ttgttcttta gcttaataaa tawgtcttat tttaaaaaaa aaaa 1614

<210> 155
<211> 99
<212> PRT
<213> Homo sapiens
<220>
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<222> -32..-1
<400> 155

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-30 -25 -20
Arg Glu Ile Arg Ile His Leu Cys Gln Arg Ser Xaa Gly Ser Gln Gly
-15 -10 -5
Val Arg Asp Phe Ile Glu Lys Arg Tyr Val Glu Leu Lys Lys Ala Asn
1 5 10 15
Pro Asp Leu Pro Ile Leu Ile Arg Glu Cys Ser Asp Val Gln Pro Lys
20 25 30
Leu Trp Ala Arg Tyr Ala Phe Gly Gln Xaa Thr Asn Val Pro Leu Asn
35 40 45
Asn Phe Ser Ala Asp Gln Val Thr Arg Xaa Leu Glu Asn Val Leu Ser
50 55 60
Gly Lys Ala
65

<210> 156
<211> 160
<212> PRT
<213> Homo sapiens
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<222> -27..-1
<400> 156

Met Gln Arg Val Ser Gly Leu Leu Ser Trp Thr Leu Ser Arg Val Leu
-25 -20 -15
Trp Leu Ser Gly Leu Ser Glu Pro Gly Ala Ala Arg Gln Pro Arg Ile
-10 -5 1 5
Met Glu Glu Lys Ala Leu Glu Val Tyr Asp Leu Ile Arg Thr Ile Arg
10 15 20
Asp Pro Glu Lys Pro Asn Thr Leu Glu Glu Leu Glu Val Val Ser Glu
25 30 35
Ser Cys Val Glu Val Gln Glu Ile Asn Glu Glu Xaa Tyr Leu Val Ile
40 45 50
Ile Arg Phe Thr Pro Thr Val Pro His Cys Ser Leu Ala Thr Leu Ile
55 60 65
Gly Leu Cys Leu Xaa Xaa Lys Leu Gln Arg Cys Leu Pro Phe Lys His
70 75 80 85
Lys Leu Xaa Ile Tyr Ile Ser Glu Gly Thr His Ser Xaa Glu Glu Asp
90 95 100
Ile Asn Xaa Gln Ile Asn Asp Lys Glu Arg Xaa Ala Xaa Ala Met Glu
105 110 115
Asn Pro Xaa Leu Arg Glu Ile Val Glu Gln Cys Val Leu Glu Pro Asp
120 125 130

<210> 157
<211> 59
<212> PRT
<213> Homo sapiens
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<222> -22..-1
<400> 157

Met Arg Leu Lys Tyr Gln His Thr Gly Ala Val Leu Asp Cys Ala Phe
-20 -15 -10

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Tyr Asp Pro Thr His Ala Trp Ser Gly Gly Leu Asp His Gln Leu Lys
    -5                   1                   5                  10
Met His Asp Leu Asn Thr Asp Gln Glu Asn Leu Val Gly Thr Met Met
                15                  20                  25
Pro Leu Ser Asp Val Leu Asn Thr Val His Lys
            30                  35
<210> 158
<211> 112
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -48..-1
<400> 158
Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly
            -45                 -40                 -35
Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala
        -30                 -25                 -20
Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala
    -15                 -10                 -5
Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val
1               5                   10                  15
Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe
            20                  25                  30
Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Xaa
        35                  40                  45
Leu Leu Met Val Ala Lys Ile Gly Val Ser Met Phe Asn Arg Pro His
    50                  55                  60
<210> 159
<211> 111
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -56..-1
<400> 159
Met Gly Gly Asn Gly Ser Thr Cys Lys Pro Asp Thr Glu Arg Gln Gly
    -55                 -50                 -45
Thr Leu Ser Thr Ala Ala Pro Thr Thr Ser Pro Ala Pro Cys Leu Ser
-40                 -35                 -30                 -25
Asn His His Asn Lys Lys His Leu Ile Leu Ala Phe Cys Ala Gly Val
                -20                 -15                 -10
Leu Leu Thr Leu Leu Leu Ile Ala Phe Ile Phe Leu Ile Ile Lys Ser
            -5                  1                   5
Tyr Arg Lys Tyr His Ser Lys Pro Gln Ala Pro Asp Pro His Ser Asp
    10                  15                  20
Pro Pro Xaa Xaa Leu Ser Ser Ile Pro Gly Glu Ser Leu Thr Tyr Ala
25                  30                  35                  40
Ser Thr Xaa Xaa Gln Thr Leu Arg Xaa Xaa Glu Xaa Xaa Leu Gly
                45                  50                  55
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<211> 144
<212> PRT
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<222> -77..-1
<400> 160
Met Ala Ala Ser Lys Val Lys Gln Asp Met Pro Pro Xaa Gly Gly Tyr
        -75                 -70                 -65
Gly Pro Ile Asp Tyr Lys Arg Asn Leu Pro Arg Arg Gly Leu Ser Gly
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    -60                 -55                 -50
Tyr Ser Met Leu Ala Ile Gly Ile Gly Thr Leu Ile Tyr Gly His Trp
-45                 -40                 -35                 -30
Ser Ile Met Lys Trp Asn Arg Glu Arg Arg Arg Leu Gln Ile Glu Asp
                -25                 -20                 -15
Phe Glu Ala Arg Ile Ala Leu Leu Pro Leu Leu Gln Ala Glu Thr Asp
            -10                 -5                  1
Arg Arg Thr Leu Gln Met Leu Arg Glu Asn Leu Glu Glu Glu Ala Ile
    5                   10                  15
Ile Met Lys Asp Val Pro Asp Trp Lys Val Gly Xaa Ser Val Xaa His
20                  25                  30                  35
Thr Thr Arg Trp Val Pro Pro Leu Ile Gly Glu Leu Tyr Gly Leu Arg
                40                  45                  50
Thr Thr Lys Glu Ala Leu His Ala Ser His Gly Phe Met Trp Tyr Thr
            55                  60                  65
<210> 161
<211> 110
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -18..-1
<400> 161
Met Glu Thr Gly Arg Leu Leu Ser Leu Ser Ser Leu Pro Leu Val Leu
            -15                 -10                 -5
Leu Gly Trp Glu Tyr Ser Ser Gln Thr Leu Asn Leu Val Pro Ser Thr
        1                   5                   10
Ser Ile Leu Ser Phe Val Pro Phe Ile Pro Leu His Leu Val Leu Phe
15                  20                  25                  30
Ala Leu Trp Tyr Leu Pro Val Pro His His Leu Tyr Pro Gln Gly Leu
                35                  40                  45
Gly Xaa His Ala Ala Xaa Ala Glu Xaa Gly Lys Arg Xaa Glu Gly Gly
            50                  55                  60
Thr Gln Xaa Ala Leu Trp Leu Arg Val Gln Pro Ser Cys Pro Ser Pro
        65                  70                  75
Val Cys Leu Glu Pro Val Pro Pro Arg Ser Arg Phe Leu Leu
    80                  85                  90
<210> 162
<211> 79
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -36..-1
<400> 162
Met Glu Leu Glu Ala Met Ser Arg Tyr Thr Ser Pro Val Asn Pro Ala
    -35                 -30                 -25
Val Phe Pro His Leu Thr Val Val Leu Leu Ala Ile Gly Met Phe Phe
-20                 -15                 -10                 -5
Thr Ala Trp Phe Phe Val Tyr Glu Val Thr Ser Thr Lys Tyr Thr Arg
                1                   5                   10
Asp Ile Tyr Lys Glu Leu Leu Ile Ser Leu Val Ala Ser Leu Phe Met
        15                  20                  25
Gly Phe Gly Val Leu Phe Leu Leu Leu Trp Val Gly Ile Tyr Val
    30                  35                  40
<210> 163
<211> 196
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
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<222> -34..-1
<400> 163
Met Ser Phe Leu Gln Asp Pro Ser Phe Phe Thr Met Gly Met Trp Ser
-30 -25 -20
Ile Gly Ala Gly Ala Leu Gly Ala Ala Ala Leu Ala Leu Leu Leu Ala
-15 -10 -5
Asn Thr Asp Val Phe Leu Ser Lys Pro Gln Lys Ala Ala Leu Glu Tyr
1 5 10
Leu Glu Asp Ile Asp Leu Lys Thr Leu Glu Lys Glu Pro Arg Thr Phe
15 20 25 30
Lys Ala Lys Glu Leu Trp Glu Lys Asn Gly Ala Val Ile Met Ala Val
35 40 45
Arg Arg Pro Gly Cys Phe Leu Cys Arg Glu Glu Ala Ala Asp Leu Ser
50 55 60
Ser Leu Lys Ser Met Leu Asp Gln Leu Gly Val Pro Leu Tyr Ala Val
65 70 75
Val Lys Xaa His Ile Xaa Thr Glu Xaa Lys Asp Phe Gln Pro Tyr Phe
80 85 90
Lys Gly Glu Ile Phe Leu Asp Glu Lys Lys Lys Phe Tyr Gly Pro Gln
95 100 105 110
Arg Arg Lys Met Met Phe Met Gly Phe Ile Arg Leu Gly Met Trp Tyr
115 120 125
Asn Phe Phe Arg Xaa Trp Asn Gly Xaa Phe Ser Gly Asn Leu Glu Gly
130 135 140
Xaa Gly Phe Ile Leu Gly Gly Ile Phe Val Val Gly Ser Xaa Lys Ala
145 150 155
Gly His Ser Ser
160
<210> 164
<211> 177
<212> PRT
<213> Homo sapiens
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<222> -18..-1
<400> 164
Met Leu Leu Cys Leu Leu Thr Pro Leu Phe Phe Met Phe Pro Thr Gly
-15 -10 -5
Phe Ser Ser Pro Ser Pro Ser Ala Ala Ala Ala Ala Gln Glu Val Arg
1 5 10
Ser Ala Thr Asp Gly Asn Thr Ser Thr Thr Pro Pro Thr Ser Ala Lys
15 20 25 30
Lys Xaa Lys Leu Asn Ser Ser Ser Ser Ser Ser Ser Asn Ser Ser Asn
35 40 45
Glu Arg Glu Asp Phe Asp Ser Thr Ser Ser Ser Ser Ser Thr Pro Pro
50 55 60
Leu Gln Pro Arg Asp Ser Ala Ser Pro Ser Thr Ser Ser Phe Cys Leu
65 70 75
Gly Val Ser Val Ala Ala Ser Ser His Val Pro Ile Xaa Lys Lys Leu
80 85 90
Arg Phe Glu Xaa Thr Leu Glu Phe Val Gly Phe Asp Ala Lys Met Ala
95 100 105 110
Glu Glu Ser Ser Ser Ser Ser Ser Ser Ser Ser Pro Thr Ala Ala Thr
115 120 125
Ser Gln Gln Gln Gln Leu Lys Asn Lys Ser Ile Leu Asn Leu Phe Cys
130 135 140
Gly Phe Gly Ala Ser Cys Lys Arg Pro Ser Gln Ile Phe Tyr His Arg
145 150 155
Leu
<210> 165
<211> 105

<212> PRT
<213> Homo sapiens
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<222> -22..-1
<400> 165
Met Gln Gly His Trp Leu Ser Ser Ala Phe Ala Leu Val Trp Leu Trp
-20 -15 -10
Leu Arg Ser Thr Gly Cys Phe Trp Trp Asp His Trp Leu Cys Lys Ser
-5 1 5 10
Arg Gln Arg Ala Val Pro Gly Cys Arg Ala Ala Leu Trp Gln Ser Ser
15 20 25
Arg Pro Gly Cys Leu Pro Ala Val Ser Gly Ser Lys Glu Arg Leu Gly
30 35 40
Phe Pro Ser Tyr Ile Trp Tyr Leu Gly Trp His Tyr Gly Asn Glu Val
45 50 55
Leu Pro Leu Trp Lys Ile His Ala Cys Arg Phe Asn Cys Arg Cys Gln
60 65 70
Phe Ala Asp Gly Arg Gln Ser Trp Ser
75 80
<210> 166
<211> 148
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -48..-1
<400> 166
Met Ile Ala Ile Tyr Gly Lys Asn Phe Cys Val Ser Ala Lys Asn Ala
-45 -40 -35
Phe Met Leu Leu Met Arg Asn Ile Val Arg Val Val Val Leu Asp Lys
-30 -25 -20
Val Thr Asp Leu Leu Leu Phe Phe Gly Lys Leu Leu Val Val Gly Gly
-15 -10 -5
Val Gly Val Leu Ser Phe Phe Phe Phe Ser Gly Arg Ile Pro Gly Leu
1 5 10 15
Gly Lys Asp Phe Lys Ser Pro His Leu Asn Tyr Tyr Trp Leu Pro Xaa
20 25 30
Met Thr Ser Ile Leu Gly Ala Tyr Val Ile Ala Ser Gly Phe Phe Ser
35 40 45
Val Phe Gly Met Cys Val Asp Thr Leu Phe Leu Cys Phe Leu Glu Asp
50 55 60
Leu Glu Arg Thr Thr Ala Pro Trp Thr Ala Leu Leu His Val Gln Glu
65 70 75 80
Leu Leu Lys Ile Leu Gly Lys Lys Asn Glu Ala Pro Pro Asp Asn Lys
85 90 95
Lys Arg Lys Xaa
100
<210> 167
<211> 259
<212> PRT
<213> Homo sapiens
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<222> -23..-1
<400> 167
Met Pro Ser Trp Ile Gly Ala Val Ile Leu Pro Leu Leu Gly Leu Leu
-20 -15 -10
Leu Ser Leu Pro Ala Gly Ala Asp Val Lys Ala Arg Ser Cys Gly Glu
-5 1 5
Val Arg Gln Ala Tyr Gly Ala Lys Gly Phe Ser Leu Ala Asp Ile Pro

10 15 20 25
Tyr Gln Glu Ile Ala Xaa Glu His Leu Arg Ile Cys Pro Gln Glu Tyr
30 35 40
Thr Cys Cys Thr Thr Glu Met Glu Asp Lys Leu Ser Gln Gln Ser Lys
45 50 55
Leu Glu Phe Glu Asn Leu Val Glu Glu Thr Ser His Phe Val Arg Thr
60 65 70
Thr Phe Val Ser Arg His Lys Lys Phe Asp Xaa Phe Phe Arg Xaa Leu
75 80 85
Xaa Glu Asn Ala Xaa Lys Ser Leu Asn Asp Xaa Phe Val Arg Thr Tyr
90 95 100 105
Gly Met Leu Tyr Xaa Gln Asn Xaa Glu Val Phe Xaa Asp Leu Phe Thr
110 115 120
Xaa Leu Lys Arg Tyr Tyr Thr Gly Gly Asn Val Asn Leu Glu Glu Met
125 130 135
Leu Asn Asp Phe Trp Ala Arg Leu Leu Glu Arg Met Phe Gln Xaa Xaa
140 145 150
Asn Pro Gln Tyr His Phe Ser Glu Asp Tyr Leu Glu Cys Val Ser Lys
155 160 165
Tyr Thr Asp Xaa Leu Lys Pro Phe Gly Asp Val Pro Arg Lys Leu Lys
170 175 180 185
Ile Gln Val Thr Arg Ala Phe Xaa Xaa Ala Arg Thr Phe Val Gln Gly
190 195 200
Leu Thr Val Gly Arg Glu Val Ala Asn Arg Val Ser Lys Val Ile Glu
205 210 215
Asn Val Leu Ser Phe Ser Leu Val Phe Leu Val Tyr Ser Val Phe Lys
220 225 230
Thr Asn Val
235
<210> 168
<211> 111
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -62..-1
<400> 168
Met Gly Glu Ser Ile Pro Leu Ala Ala Pro Val Pro Val Glu Gln Ala
-60 -55 -50
Val Leu Glu Thr Phe Phe Ser His Leu Gly Ile Phe Ser Tyr Asp Lys
-45 -40 -35
Ala Lys Asp Asn Val Glu Lys Glu Arg Glu Ala Asn Lys Ser Ala Gly
-30 -25 -20 -15
Gly Ser Trp Leu Ser Leu Leu Ala Ala Leu Ala His Leu Ala Ala Ala
-10 -5 1
Glu Lys Val Tyr His Ser Leu Thr Tyr Leu Gly Gln Lys Leu Gly Thr
5 10 15
Ser Ala Pro Pro Pro Glu Pro Leu Glu Glu Glu Val Lys Gly Val Tyr
20 25 30
Ser Pro Xaa Gly Ser Gly Leu Gly Xaa Pro Ser Leu Cys His Phe
35 40 45
<210> 169
<211> 311
<212> PRT
<213> Homo sapiens
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<223> SIGNAL
<222> -23..-1
<400> 169
Met Ala Asp Val Ile Asn Val Ser Val Asn Leu Glu Ala Phe Ser Gln
-20 -15 -10

Ala Ile Ser Ala Ile Gln Ala Leu Arg Ser Ser Val Ser Arg Val Phe
-5 1 5
Asp Cys Leu Lys Asp Gly Met Arg Asn Lys Glu Thr Leu Glu Gly Arg
10 15 20 25
Glu Lys Ala Phe Ile Ala His Phe Gln Asp Asn Leu His Ser Val Asn
30 35 40
Arg Asp Leu Asn Glu Leu Glu Arg Leu Ser Asn Leu Val Gly Xaa Pro
45 50 55
Ser Glu Asn His Pro Leu His Asn Ser Gly Leu Leu Xaa Leu Asp Pro
60 65 70
Val Gln Asp Lys Thr Pro Leu Tyr Ser Gln Leu Leu Gln Ala Tyr Lys
75 80 85
Trp Ser Asn Lys Leu Gln Tyr His Ala Gly Leu Ala Ser Gly Leu Leu
90 95 100 105
Asn Xaa Gln Ser Xaa Lys Arg Xaa Ala Asn Gln Met Gly Val Ser Ala
110 115 120
Lys Arg Arg Pro Lys Ala Gln Pro Thr Thr Leu Val Leu Pro Pro Gln
125 130 135
Tyr Val Asp Asp Val Ile Ser Arg Ile Asp Arg Met Phe Pro Glu Met
140 145 150
Ser Ile His Leu Ser Arg Pro Asn Gly Thr Ser Ala Met Leu Leu Val
155 160 165
Thr Leu Gly Lys Val Leu Lys Val Xaa Val Val Xaa Arg Xaa Leu Phe
170 175 180 185
Ile Asp Arg Thr Ile Val Lys Gly Tyr Xaa Glu Asn Val Tyr Xaa Glu
190 195 200
Xaa Gly Xaa Leu Asp Ile Trp Ser Lys Ser Asn Tyr Gln Val Phe Gln
205 210 215
Lys Val Thr Asp His Ala Thr Thr Ala Leu Leu His Xaa Xaa Leu Pro
220 225 230
Gln Met Pro Asp Val Val Val Arg Ser Phe Xaa Thr Trp Leu Arg Ser
235 240 245
Tyr Ile Lys Leu Phe Gln Ala Pro Cys Gln Arg Cys Gly Lys Phe Leu
250 255 260 265
Gln Asp Gly Leu Pro Pro Thr Trp Arg Asp Phe Arg Thr Leu Glu Ala
270 275 280
Phe His Asp Thr Cys Arg Gln
285

<210> 170
<211> 91
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -60..-1
<400> 170
Met Thr Ser Leu Phe Ala Val Val Leu Gln Arg Glu Lys Glu Pro His
-60 -55 -50 -45
Leu Trp Leu Ser Ser Pro His Ile Arg Phe Ser Leu Arg Val Asn Lys
-40 -35 -30
Leu Ser Glu Leu Met Leu Gln Leu Leu Gln Phe Lys Ala Phe Pro Ser
-25 -20 -15
Ser Leu Val Pro Phe Phe Leu Phe Thr Cys Phe Gly His Phe Pro Ser
-10 -5 1
Phe Thr Thr Phe Gln Gly Phe Ile Glu Asn Asn Leu Leu Gln Asn Gln
5 10 15 20
Phe Asn Ser Asn Val Asp Ile Val Ala Cys Ser
25 30

<210> 171
<211> 287
<212> PRT

<213> Homo sapiens
<220>
<223> SIGNAL
<222> -17..-1
<400> 171

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Met Glu Leu Glu Arg Ile Val Ser Ala Ala Leu Leu Ala Phe Val Gln
       -15                 -10                 -5
Thr His Leu Pro Glu Ala Asp Leu Ser Gly Leu Asp Glu Val Ile Phe
    1               5                  10                  15
Ser Tyr Val Leu Gly Val Leu Glu Asp Leu Gly Pro Ser Gly Pro Ser
                20                  25                  30
Glu Glu Asn Phe Asp Met Glu Ala Phe Thr Glu Met Met Glu Ala Tyr
            35                  40                  45
Val Pro Gly Phe Ala His Ile Pro Arg Gly Thr Ile Gly Asp Met Met
        50                  55                  60
Gln Lys Leu Ser Gly Gln Leu Ser Asp Ala Xaa Asn Lys Glu Asn Leu
    65                  70                  75
Gln Pro Gln Asn Ser Gly Val Gln Gly Gln Val Pro Ile Ser Pro Glu
80                  85                  90                  95
Pro Leu Gln Arg Pro Glu Met Leu Lys Glu Glu Thr Arg Ser Ser Ala
                100                 105                 110
Ala Ala Ala Ala Asp Thr Gln Asp Glu Ala Thr Gly Ala Glu Glu Glu
            115                 120                 125
Leu Leu Pro Gly Val Asp Val Leu Leu Glu Val Phe Pro Thr Cys Ser
        130                 135                 140
Val Glu Gln Ala Gln Trp Val Leu Ala Lys Ala Arg Gly Asp Leu Glu
    145                 150                 155
Glu Ala Val Gln Met Leu Val Glu Gly Lys Glu Glu Gly Pro Ala Ala
160                 165                 170                 175
Trp Glu Gly Pro Asn Gln Asp Leu Pro Arg Arg Leu Arg Gly Pro Gln
                180                 185                 190
Lys Asp Glu Leu Lys Ser Phe Ile Leu Gln Lys Tyr Met Met Val Asp
            195                 200                 205
Ser Ala Glu Asp Gln Lys Ile His Arg Pro Met Ala Pro Lys Glu Ala
        210                 215                 220
Pro Lys Lys Leu Ile Arg Tyr Ile Asp Asn Gln Val Val Ser Thr Lys
    225                 230                 235
Gly Glu Arg Phe Lys Asp Val Arg Asn Pro Glu Ala Glu Glu Met Lys
240                 245                 250                 255
Ala Thr Tyr Ile Asn Leu Lys Pro Ala Arg Lys Tyr Arg Phe His
                260                 265                 270
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<210> 172
<211> 104
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -49..-1
<400> 172

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Met Glu His Leu Thr His Ser Ser Gln Lys Leu Gln Ala Asp Glu His
                -45                 -40                 -35
Leu Thr Lys Glu Val Trp Ser Arg Leu Leu Lys Glu Lys Gly Pro Ala
            -30                 -25                 -20
Gly Leu Ile Leu Cys Phe Leu Cys Leu Tyr Pro Ile Pro Leu Cys Thr
        -15                 -10                 -5
Ser His Pro Val Xaa Leu Cys Ala His Pro Gln Asp Val Tyr Pro Val
    1               5                  10                  15
Val Val Arg Ala Glu Ile His Ala Glu Leu Tyr Gln Glu Leu Ala Tyr
                20                  25                  30
Leu Lys Thr Glu Thr Glu Ser Leu Ala His Leu Phe Ala Leu Val Pro
            35                  40                  45
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Gln Ala Lys Ile Lys Asn Arg Val
50 55
<210> 173
<211> 84
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -36..-1
<400> 173
Met Gly Leu Leu Thr Phe Gly Tyr Ile Glu Xaa Xaa Xaa Lys Thr Glu
-35 -30 -25
His Asn Pro Asp His His Ser Cys Leu Ala Val Ser Trp Glu Ala Ala
-20 -15 -10 -5
Gly Cys His Gly Ala Gly Thr Gln Gln Ser Pro Leu Gly Val Ala Gly
1 5 10
Pro Trp Arg Pro Arg Pro Pro Cys Val Gly Ser Leu Leu Ala Ala Arg
15 20 25
Ser Leu His Lys Gln Val Ile Leu Phe Gly Leu Leu Gly Phe Ala Tyr
30 35 40
Asp His Ala Ala
45
<210> 174
<211> 131
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -20..-1
<400> 174
Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser
-20 -15 -10 -5
Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp
1 5 10
Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp
15 20 25
Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Xaa Xaa Leu Xaa Lys
30 35 40
Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Xaa
45 50 55 60
Cys Pro His Ser Gln Ala Leu Lys Lys Xaa Phe Ala Glu Asn Lys Xaa
65 70 75
Ile Gln Lys Leu Ala Xaa Gln Phe Val Xaa Leu Asn Leu Val Tyr Glu
80 85 90
Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Xaa Pro Xaa Asp
95 100 105
Tyr Val Cys
110
<210> 175
<211> 131
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -23..-1
<400> 175
Met Met Asn Phe Arg Gln Arg Met Gly Trp Ile Gly Val Gly Leu Tyr
-20 -15 -10
Leu Leu Ala Ser Ala Ala Ala Phe Tyr Tyr Val Phe Glu Ile Ser Glu
-5 1 5
Thr Tyr Asn Arg Leu Ala Leu Glu His Ile Gln Gln His Pro Gly Glu

10 15 20 25
Pro Leu Glu Gly Thr Thr Trp Thr His Ser Leu Lys Ala Gln Leu Leu
30 35 40
Ser Leu Pro Phe Trp Val Trp Thr Val Ile Phe Leu Val Pro Tyr Leu
45 50 55
Gln Xaa Phe Leu Phe Leu Tyr Ser Cys Thr Lys Xaa Asp Pro Lys Thr
60 65 70
Val Gly Tyr Cys Xaa Ile Pro Ile Cys Leu Ala Xaa Ile Xaa Asn Arg
75 80 85
His Gln Asp Phe Val Lys Ala Ser Asn Gln Ile Ser Lys Leu Gln Leu
90 95 100 105
Ile Asp Thr
<210> 176
<211> 335
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -16..-1
<400> 176
Met Ala Val Phe Val Val Leu Leu Ala Leu Val Ala Gly Val Leu Gly
-15 -10 -5
Asn Glu Phe Ser Ile Leu Lys Ser Pro Gly Ser Val Val Phe Arg Asn
1 5 10 15
Gly Asn Trp Pro Ile Pro Gly Glu Arg Ile Pro Asp Val Ala Ala Leu
20 25 30
Ser Met Gly Phe Ser Val Lys Glu Asp Leu Ser Trp Pro Gly Leu Ala
35 40 45
Val Gly Asn Leu Phe His Arg Pro Arg Ala Ser Val Met Val Met Val
50 55 60
Lys Gly Val Asn Asn Xaa Pro Leu Pro Pro Gly Cys Val Ile Ser Tyr
65 70 75 80
Pro Leu Glu Asn Ala Val Pro Phe Ser Leu Asp Ser Val Ala Asn Ser
85 90 95
Ile His Ser Leu Phe Ser Glu Glu Thr Pro Val Val Leu Gln Leu Ala
100 105 110
Pro Ser Glu Glu Arg Val Tyr Met Val Gly Lys Ala Asn Ser Val Trp
115 120 125
Lys Thr Phe Gln Ser Leu Ala Pro Ala Pro Xaa Ile Xaa Cys Phe Lys
130 135 140
Lys Thr Leu Phe Ser Val His Ser Pro Xaa Ile Xaa Leu Ser Arg Asn
145 150 155 160
Asn Glu Val Asp Xaa Leu Phe Leu Ser Glu Leu Gln Val Leu His Asp
165 170 175
Ile Ser Ser Leu Leu Ser Arg His Lys His Leu Ala Lys Asp His Ser
180 185 190
Pro Asp Leu Tyr Ser Leu Glu Leu Ala Gly Leu Asp Glu Ile Gly Lys
195 200 205
Arg Tyr Gly Glu Asp Ser Glu Gln Phe Arg Asp Ala Ser Lys Ile Leu
210 215 220
Val Asp Ala Leu Gln Lys Phe Ala Asp Asp Met Tyr Ser Leu Tyr Gly
225 230 235 240
Gly Asn Ala Val Val Glu Leu Val Thr Val Lys Ser Phe Asp Thr Ser
245 250 255
Leu Ile Arg Lys Thr Arg Thr Ile Leu Glu Ala Lys Gln Ala Lys Asn
260 265 270
Pro Ala Ser Pro Tyr Asn Leu Ala Tyr Lys Tyr Asn Phe Glu Tyr Ser
275 280 285
Val Val Phe Asn Met Val Leu Trp Ile Met Ile Ala Leu Ala Leu Ala
290 295 300
Val Ile Ile Thr Ser Tyr Asn Ile Trp Asn Met Glu Ser Trp Ile

305 310 315
<210> 177
<211> 84
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -55..-1
<400> 177
Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile Gly Leu
-55 -50 -45 -40
Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys
-35 -30 -25
Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu
-20 -15 -10
Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val
-5 1 5
Ser Asn Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg
10 15 20 25
Met Ile Ser Cys
<210> 178
<211> 280
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -18..-1
<400> 178
Met Glu Gly Pro Arg Gly Trp Leu Val Leu Cys Val Leu Ala Ile Ser
-15 -10 -5
Leu Ala Ser Met Val Thr Glu Asp Leu Cys Arg Ala Pro Asp Gly Lys
1 5 10
Lys Gly Glu Ala Gly Arg Pro Gly Arg Arg Gly Arg Pro Gly Leu Lys
15 20 25 30
Gly Glu Gln Gly Glu Pro Gly Ala Pro Gly Ile Arg Thr Gly Ile Gln
35 40 45
Gly Leu Lys Gly Asp Gln Gly Glu Pro Gly Pro Ser Gly Asn Pro Gly
50 55 60
Lys Val Gly Tyr Pro Gly Pro Ser Gly Pro Leu Gly Ala Arg Gly Ile
65 70 75
Pro Gly Ile Lys Gly Thr Lys Gly Ser Pro Gly Asn Ile Lys Asp Gln
80 85 90
Pro Arg Pro Ala Phe Ser Ala Ile Arg Arg Asn Pro Pro Met Gly Gly
95 100 105 110
Asn Val Val Ile Phe Asp Thr Val Ile Thr Asn Gln Glu Glu Pro Tyr
115 120 125
Gln Asn His Ser Gly Arg Phe Val Cys Thr Val Pro Ala Thr Thr Thr
130 135 140
Ser Pro Ser Arg Cys Cys Pro Ser Gly Lys Ser Ala Cys Pro Ser Ser
145 150 155
Pro Pro Gln Gly Ala Arg Ser Asp Ala Pro Trp Ala Ser Val Thr Pro
160 165 170
Pro Thr Arg Gly Ser Ser Arg Trp Cys Gln Gly Ala Trp Cys Phe Ser
175 180 185 190
Cys Ser Arg Val Thr Arg Ser Gly Leu Lys Lys Thr Pro Lys Arg Val
195 200 205
Thr Phe Thr Arg Ala Leu Arg Pro Thr Ala Ser Ser Ala Ala Ser Ser
210 215 220
Ser Ser His Leu Pro Glu Pro Gly Lys Asp Pro Leu Pro His Pro Pro
225 230 235
Leu Trp Leu Pro Cys Ser Ala Cys Lys Met Gly Ala Leu Leu Leu Gln

240 245 250
Leu Leu Lys Gly Gly Gly Trp Leu
255 260
<210> 179
<211> 140
<212> PRT
<213> Homo sapiens
<220>
<223> SIGNAL
<222> -51..-1
<400> 179
Met Arg Lys Asp Pro Ser Gly Ala Gly Leu Trp Leu His Ser Gly Gly
-50 -45 -40
Pro Val Leu Pro Tyr Val Arg Glu Ser Val Arg Arg Asn Pro Ala Ser
-35 -30 -25 -20
Ala Ala Thr Pro Ser Thr Ala Val Gly Leu Phe Pro Ala Pro Thr Glu
-15 -10 -5
Cys Phe Ala Arg Val Ser Cys Ser Gly Val Glu Ala Leu Gly Arg Arg
1 5 10
Asp Trp Leu Gly Gly Gly Pro Arg Ala His Xaa Xaa Ala Thr Glu Xaa
15 20 25
Ser Ala Pro Lys Glu Ser Leu Gly Cys His Asp Cys His Ala Ile Lys
30 35 40 45
Lys Cys Arg Lys Trp Glu Val Phe Arg Met Thr His Gln Val Leu Phe
50 55 60
Pro Arg Val Trp Ala Leu Ser Trp Asn Pro Leu Ala Cys Thr Pro Ser
65 70 75
Cys Leu Gln Arg Cys Thr Cys Ile Pro Xaa Cys Ser
80 85
<210> 180
<211> 92
<212> PRT
<213> Homo sapiens
<400> 180
Met Ala Pro Leu His His Ile Leu Val Phe Cys Val Gly Leu Leu Thr
1 5 10 15
Met Ala Lys Ala Glu Ser Pro Lys Glu His Asp Pro Phe Thr Tyr Asp
20 25 30
Tyr Gln Ser Leu Gln Ile Gly Gly Leu Val Ile Ala Gly Ile Leu Phe
35 40 45
Ile Leu Gly Ile Leu Ile Val Leu Ser Arg Arg Cys Arg Cys Lys Phe
50 55 60
Asn Gln Gln Gln Arg Thr Gly Glu Pro Asp Glu Glu Glu Gly Thr Phe
65 70 75 80
Arg Ser Ser Ile Arg Arg Leu Ser Thr Arg Arg Arg
85 90
<210> 181
<211> 240
<212> PRT
<213> Homo sapiens
<400> 181
Leu Leu Ser Arg Thr Val Arg Thr Gln Ile Leu Thr Gly Lys Glu Leu
1 5 10 15
Arg Val Ala Thr Gln Glu Lys Glu Gly Ser Ser Gly Arg Cys Met Leu
20 25 30
Thr Leu Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly
35 40 45
Ala Cys Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly
50 55 60
Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly
65 70 75 80

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Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile Arg Glu
                85                  90                  95
Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe Ser Asp
            100                 105                 110
Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met Thr Ala
        115                 120                 125
Tyr Leu Asp Leu Leu Leu Gly Asn Cys Tyr Leu Met Pro Leu Asn Thr
    130                 135                 140
Ser Ile Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly Lys Leu
145                 150                 155                 160
Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu Asp Leu
                165                 170                 175
Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile Phe Ile
            180                 185                 190
Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg Arg Asp
        195                 200                 205
Leu Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp Lys Ile
    210                 215                 220
Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys Gln Glu
225                 230                 235                 240
<210> 182
<211> 245
<212> PRT
<213> Mus musculus
<400> 182
Glu Leu Cys Pro Gly Val Asn Thr Gln Pro Tyr Leu Cys Glu Thr Gly
 1               5                  10                  15
His Cys Cys Gly Glu Thr Gly Cys Cys Thr Tyr Tyr Tyr Glu Leu Trp
            20                  25                  30
Trp Phe Trp Leu Leu Trp Thr Val Leu Ile Leu Phe Ser Cys Cys Cys
        35                  40                  45
Ala Phe Arg His Arg Arg Ala Lys Leu Arg Leu Gln Gln Gln Gln Arg
    50                  55                  60
Gln Arg Glu Ile Asn Leu Leu Ala Tyr His Gly Ala Cys His Gly Ala
65                  70                  75                  80
Gly Pro Val Pro Thr Gly Ser Leu Leu Asp Leu Arg Leu Leu Ser Ala
                85                  90                  95
Phe Lys Pro Pro Ala Tyr Glu Asp Val Val His His Pro Gly Thr Pro
            100                 105                 110
Pro Pro Pro Tyr Thr Val Gly Pro Gly Tyr Pro Trp Thr Thr Ser Ser
        115                 120                 125
Glu Cys Thr Arg Cys Ser Ser Glu Ser Ser Cys Ser Ala His Leu Glu
    130                 135                 140
Gly Thr Asn Val Glu Gly Val Ser Ser Gln Gln Ser Ala Leu Pro His
145                 150                 155                 160
Gln Glu Gly Glu Pro Arg Ala Gly Leu Ser Pro Val His Ile Pro Pro
                165                 170                 175
Ser Cys Arg Tyr Arg Arg Leu Thr Gly Asp Ser Gly Ile Glu Leu Cys
            180                 185                 190
Pro Cys Pro Asp Ser Ser Glu Gly Glu Pro Leu Lys Glu Ala Arg Ala
        195                 200                 205
Ser Ala Ser Gln Pro Asp Leu Glu Asp His Ser Pro Cys Ala Leu Pro
    210                 215                 220
Pro Asp Ser Val Ser Gln Val Pro Pro Met Gly Leu Ala Ser Ser Cys
225                 230                 235                 240
Gly Thr Ser His Lys
                245
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